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(71) Applicant: DAVID SARNOFF RESEARCH CENTER, INC. [US/US]; 201 Washington Road, CN5300, Princeton, NJ 08543-5300 (US).

(72) Inventors: ZANZUCCHI, Peter, J.; 13 Jill Drive, Lawrenceville, NJ 08648 (US). BURTON, Charlotte, A.; 555 Duquesne Boulevard, Brick, NJ 08723 (US). MCBRIDE, Sterling, E.; 4114 Fieldcrest Court, Lawrenceville, NJ 08648 (US). DEMERS, Robert; 26 Evans Drive, Cranbury, NJ 08512 (US).

(74) Agent: BURKE, William, J.; David Sarnoff Research Center, Inc., 201 Washington Road, CN5300, Princeton, NJ 08543-5300 (US).

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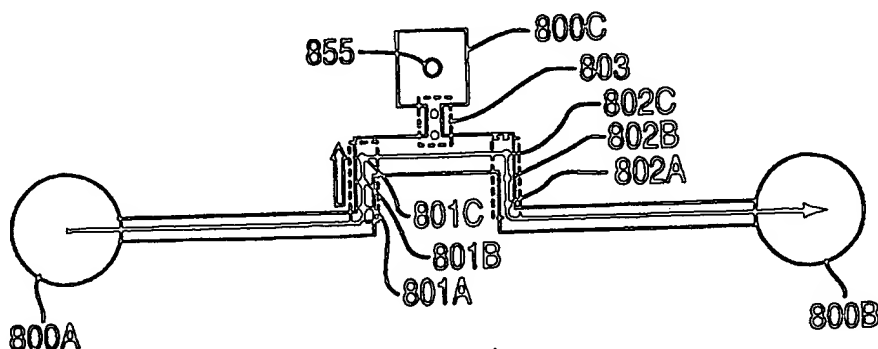
(57) Abstract

The invention provides electrode-based pumps (803) and methods of operating such pumps. In one embodiment, the invention provides an electrode-based pump situated in a fluid channel comprising a first electrode (801A) and a second electrode (801B), wherein the first (801A) and second (801B) electrodes have a diameter from about 25 microns to about 100 microns and are spaced from about 100 microns to about 2,500 microns apart. In another embodiment, the invention provides an electrode-based pump comprising a first electrode (801A), second electrode (801B) and third electrode (801C).

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ELECTROKINETIC PUMPING

This application relates to electrode-based pumps, methods of operating such pumps, and calibration devices for such pumps.

Recently, a number of academic articles have focused on the
5 problems associated with conducting chemical reactions on a micro-scale. This literature has discussed the possibility of managing such reactions on wafer-sized solid supports that have been etched to create microchannels. Reactor systems of this scale could allow multiple diagnostic or drug screening assays to be conducted in a transportable device that uses small
10 amounts of reagents, thus reducing supply and disposal costs.   -

One mechanism for developing new drugs not provided for by nature has been dubbed "rational" drug design. This process looks at the structures of biological macromolecules as determined by crystallography and at the structures of pharmacological agents known to interact with these
15 macromolecules. With the use of computer workstations, it was hoped that new pharmacological agents could be designed that had appropriately positioned functionalities for strongly interacting with the macromolecule. One difficulty with this approach is that growing crystals appropriate for crystallographic structural determinations is a tedious, empirical science. In
20 many cases, it is unclear if appropriate crystals can be grown (for instance, for the glycoprotein hormones such a chorionic gonadotropin or other glycoproteins). Another difficulty is that chemistry does not provide the malleable construction tools evoked by the phrase "design"; instead, chemical building blocks provide only a limited number of bond angles and lengths. For
25 example, the structural routes by which a chlorine group might be positioned in particular part of a drug-binding pocket in the macromolecule may be many, while the advantages or disadvantages of the ancillary structures needed to position this group are hard to "rationally" evaluate.

Combinatorial chemistry seeks to create its own
30 "evolutionary" proc ss that selects for compounds with the desired pharmac logical activity. The key to making the process evolutionary is to generate large families of "mutants", in this cas families f compounds with

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some chemical relatedness but with clear differences. The concepts of rational design may be taken advantage of in selecting the families of compounds to be explored by the combinatorial method.

Combinatorial chemistry seeks to generate new leads to

5 classes of compounds that have potential pharmacological activity. Traditionally, such leads have been found by screening various plant or animal extracts for pharmacological activity. Such extracts are tedious to obtain, may have very small concentrations of potentially useful compounds, and at best only contain compounds selected by evolutionary pressures that may

10 have nothing to do with the disease that is sought to be treated. After an extract has been identified, the process provides little information as to the identity of the active ingredient.

Combinatorial chemistry seeks to create the large family of compounds by permutation of a relatively limited set of building block

15 chemicals. Preferably, the combinatorial method will create identifiable pools containing one or more synthetic compounds. These pools need not be identifiable by the chemical structure of the component compounds, but should be identifiable by the chemical protocol that created the compounds. These pools are then screened in an assay that is believed to correlate with a

20 pharmacological activity. Those pools that produce promising results are examined further to identify the component compounds and to identify which of the component compounds are responsible for the results.

The follow-up protocol used to identify the active compounds in a combinatorial pool can also involve a combinatorial method. For instance,

25 the promising pool could result from the reaction, first, of a mixture of compounds A, B and C, which compounds do not react with one another, with compounds D, E and F, which compounds do not react with one another but do react with compounds A, B or C. Second, the resulting compounds are reacted with compounds G, H and I. To narrow the possible identity of

30 the active compounds in the pool, the A-D, A-E, A-F, B-D, B-E, B-F, C-D, C-E and C-F products can be separately created by combinatorial chemistry and separately reacted with a the mixture of G, H and I. After this step, the

sub-pool that is active in the screening assay generally will contain a more limited family of compounds.

Once promising molecules are identified by combinatorial chemistry, the identified molecules provide information that aides in the
5 design of further combinatorial experiments. The full array of promising compounds identified by combinatorial chemistry can provide valuable information to guide traditional pharmaceutical chemistry efforts.

A popular tool in the emerging field of combinatorial chemistry is to attach the first chemical building blocks to a solid support,
10 typically a glass or polymeric support, such as the supports used in the well known Merrifield method for synthesizing polypeptides. This attachment provides a mechanism for quickly isolating product by simply washing away reactants and related impurities and decoupling the product from the support. In some cases, the support-coupled product can be assayed for
15 pharmacological activity.

Miniaturization is usefully employed in combinatorial chemistry since: (i) workers generally seek compounds that are pharmacologically active in small concentrations; (ii) in creating a vast "evolutionary" assortment of candidate molecules it is preferable to have the
20 numerous reactions well documented and preferably under the direction of a limited number of workers to establish reproducibility of technique; (iii) it is expensive to create a vast, traditionally-scaled synthetic chemistry complex for creating a sufficiently varied family of candidate compounds; and (iv) substantial concerns are raised by the prospect of conducting assays of the
25 products of combinatorial chemistry at more standard reaction scales. Miniaturization allows for the economic use of robotic control, thereby furthering reproducibility.

The wafer-sized devices described above can be ideal for combinatorial chemistry, allowing for numerous synthetic chemistry reactions
30 to be conducted substantially under computer control using only small quantities of reagents. However, the acad mic literatur advocating such micro-scale devices has not adequately addressed fundamental issues in

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conducting combinatorial chemistry at this scale: for instance, how does one
manage to effectively pump fluids in such a device to the multitude of
microscaled reaction cells (e.g., 100 to 100,000) in the device? The present
invention provides a pump that can be incorporated within such devices.

5   SUMMARY OF THE INVENTION

The invention provides electrode-based pumps and methods
and devices for operating such pumps. In one embodiment, the invention
provides an electrode-based pump situated in a fluid channel comprising a
first electrode and a second electrode, wherein the first and second electrodes

10   have a diameter from about 25 microns to about 100 microns and are spaced
from about 100 microns to about 2,500 microns apart. In another
embodiment, the invention provides an electrode-based pump comprising a
first electrode, second electrode and third electrode.

BRIEF DESCRIPTION OF THE DRAWINGS

15   Figure 1 shows a voltage pulse pattern used to power an
electrode-based pump useful in the liquid distribution system of the invention.

Figures 2A and 2B show the field strength and orientation at
numerous points about electrode-based pumps.

Figure 3 shows a calibration device.

20   Figure 4 shows another calibration device.

Figure 5 displays a cut-away view of a liquid distribution
system that can be used with the invention.

Figure 6 displays a distribution plate of the liquid distribution
system of Figure 5.

25   Figure 7 displays an expanded view of a portion of the
distribution plate of Figure 6.

Figure 8 shows a capillary barrier between a first distribution
channel and a buffer channel.

Figures 9A - 9D show various capillary barrier designs.

30   Figure 10 shows a device for conducting field assisted
bonding of plates.

5

Figure 11 shows a digital driver for powering the electrode-based pumps.

Figures 12A and 12B show a channel device having electrode-based pumps.

5

Figure 13 shows a liquid distribution system design pursuant hydrologic liquid distribution system.

Figure 14 shows a reaction cell having a heater and a thermocouple.

Figures 15A and 15B show a valve design.

10

DEFINITIONS

The following terms shall have the meaning set forth below:

- addressable   a reaction cell or channel is "addressable" by a reservoir or another channel if liquid from the reservoir or other channel can be directed to the reaction cell or channel.

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○ adjacent

"adjacent" as used in these situations: (i) a first structure in one of the plates is adjacent to a second structure in the same or another plate if the vertical projection of the first structure onto the plate of the second structure superimposes the first structure on the second or places it within about 250 μm of the second; and (ii) groupings of two or more channels are adjacent to one another if each channel is in substantially the same horizontal plane, and all but the outside two channels in the grouping are adjacent (in the sense defined in (i) above) to two neighbor channels in the grouping. Preferably, under item (i), a first structure is adjacent to a second structure if the vertical projection of the first structure onto the plate of the second structure superimposes the first structure on the second or places it within about 150 μm of the second.

○ capillary dimensions

dimensions that favor capillary flow of a liquid. Typically, channels of capillary dimensions are no wider than about 1.5 mm. Preferably channels are no wider than about 500 μm, yet more preferably no wider than about 250 μm, still more preferably no wider than about 150μm.

○ capillary barrier	a barrier to fluid flow in a channel comprising an opening of the channel into a larger space designed to favor the formation, by liquid in the channel, of an energy minimizing liquid surface such as a meniscus at the opening. Preferably, capillary barriers include a dam that raises the vertical height of the channel immediately before the opening into the larger space.
○ connected	the channels, reservoirs and reaction cells of the invention are "connected" if there is a route allowing fluid between them, which route does not involve using a reaction cell as part of the link.
○ directly connected	reservoirs and horizontal channels are "directly connected" if they are connected and either (1) no other channel is interposed between them or (2) only a single vertical channel is interposed between them.
○ flow preference	the direction that a liquid pumps under the influence of an electrode-based pump having two symmetrically situated rod-shaped electrodes.
○ hole diameter	because techniques for fabricating small holes often create holes that are wider at one end than the other (for instance, about 50 microns wider), the hole diameter values recited to herein refer to the narrowest diameter.

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○ horizontal, vertical, EW, NS	indications of the orientation of a part of the distribution system refer to the orientation when the device is in use. The notations "EW axis" and "NS axis" are in reference to Figures 1, 2, 3 and 7, where an EW axis goes from right to left and is perpendicular to the long axis of the page and a NS axis is from top to bottom parallel to the long axis of the page.
○ independent	channels, reservoirs or reaction cells that are not connected.
○ offset	two sets of channels are "offset" when none of the channels in the first such set is adjacent to any of the channels in the second set.
○ perpendicular	channels in the distribution plate are perpendicular even if primarily located on separate horizontal planes if their vertical projections onto the same horizontal plane are perpendicular.
○ reservoir	unless a different meaning is apparent from the context, the terms "reservoir" and "fluid reservoir" include the horizontal extension channels (sometimes simply termed "extensions") directly connected to the reservoir or fluid reservoir.
○ second reservoir extension channels	these extension channels include the distribution channels that may branch off of these extension channels.

5

o substantially the length of one of the horizontal dimensions	at least about 70% of one of the major horizontal dimensions (e.g. the EW or NS dimensions illustrated in the Figures) of the distribution plate.
o U-plumbing channel	a channel designed to connect at least two channels or reservoirs such that the liquid level in one of the connected channels or reservoirs will equalize with the liquid level in the other connected channel or reservoirs due to hydrological forces. U-plumbing channels typically have vertical channels that connect channels or reservoirs located in a higher vertical plane with a substantially horizontal channel segment of the U-plumbing channel located in a lower plane -- these vertical and horizontal segments together comprise the U-plumbing channel. The feeder channels of the invention are typically U-plumbing channels.

5   DETAILED DESCRIPTION

A. Electrode-based Pumps

At least two types of such electrode-based pumping has been described, typically under the names "electrohydrodynamic pumping" (EHD) and "electroosmosis" (EO). EHD pumping has been described by Bart

10   et al., "Microfabricated Electrohydrodynamic Pumps," *Sensors and Actuators*, A21-A23: 193-197, 1990 and Richter et al., "A Micromachined Electrohydrodynamic Pump," *Sensors and Actuators*, A29:159-168, 1991. EO pumps have been described by Dasgupta et al., "Electroosmosis: A Reliable Fluid Propulsion System for Flow Injection Analysis," *Anal. Chem.*,

15   66: 1792-1798, 1994. In the present application, pumping effected with electrodes is termed "electrokinetic pumping."

10

EO pumping is believed to take advantage of the principle
that the surfaces of many solids, including quartz, glass and the like, become
charged, negatively or positively, in the presence of ionic materials, such as
salts, acids or bases. The charged surfaces will attract oppositely charged

5   counter ions in solutions of suitable conductivity. The application of a voltage
to such a solution results in a migration of the counter ions to the oppositely
charged electrode, and moves the bulk of the fluid as well. The volume flow
rate is proportional to the current, and the volume flow generated in the fluid
is also proportional to the applied voltage. Typically, in channels of capillary

10   dimensions, the electrodes effecting flow can be spaced further apart than in
EHD pumping, since the electrodes are only involved in applying force, and
not, as in EHD, in creating charges on which the force will act. EO pumping
is generally perceived as a method appropriate for pumping conductive
solutions.

15   EHD pumps have typically been viewed as suitable for
moving fluids of extremely low conductivity, e.g., 10^{-14} to 10^{-9} S/cm. It has
now been demonstrated herein that a broad range of solvents and solutions
can be pumped using appropriate solutes than facilitate pumping, using
appropriate electrode spacings and geometries, or using appropriate pulsed or

20   d.c. voltages to power the electrodes, as described further below.

             The electrodes of first pumps 360 and second pumps 361
used in the liquid distribution system described below preferably have a
diameter from about 25 microns to about 100 microns, more preferably from
about 50 microns to about 75 microns. Preferably, the electrodes protrude

25   from the top of a channel to a depth of from about 5 % to about 95 % of the
depth of the channel, more preferably from about 25 % to about 50 % of the
depth of the channel. Usually, as a result the electrodes, defined as the
elements that interact with fluid, are from about 5 microns to about 95
microns in length, preferably from about 25 microns about to 50 microns.

30   Preferably, a pump includes an alpha electrode 364 (such as first electrode
360A or third electrode 361A) and a beta electrode 365 (such as third
electrod 360B and f urth electrode 361B) that are preferably spaced from

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about 100 microns to about 2,500 microns apart, more preferably, from about 150 microns to about 1000 microns apart, yet more preferably from about 250 microns to about 1000 microns apart, or, in an alternate embodiment, from about 150 microns to about 250 microns apart. The

5   separation of electrodes shall be measured from the center points of the electrodes as they first protrude into their associated fluid channel. In a particularly preferred embodiment, a gamma electrode 366 (not shown) is spaced from about 200 microns to about 5,000 microns, more preferably from about 500 microns to about 1,500 microns, yet more preferably about

10 1,000 microns from the farther of the alpha electrode 364 and the beta electrode 365. In an alternative preferred embodiment, the pump has two additional electrodes comprising a gamma electrode 366 (not shown) and a delta electrode 367 that are spaced from about 200 microns to about 5,000 microns, more preferably from about 500 microns to about 1,500 microns,

15 yet more preferably about 1,000 microns apart. Where the electrodes are located in fluid channels that have bends, the distances are measured along a line that defines the center line of the fluid channel. In contexts where relatively low conductivity fluids are pumped, voltages are applied across the alpha electrode 364 and the beta electrode 365, while in contexts where

20 relatively more highly conductive fluids are pumped the voltage is induced between gamma electrode 366 and one of alpha electrode 364, beta electrode 365 or delta electrode 367. The latter circumstance typically applies for solvents traditionally pumped with EO pumping, although this invention is not limited to any theory that has developed around the concepts

25 of EHD or EO pumping. No firm rules dictate which electrode combination is appropriate for a given solvent or solution; instead an appropriate combination can be determined empirically in light of the disclosures herein.

The voltages used across alpha and beta electrodes 364 and 365 when the pump is operated in d.c. mode are typically from about 40 V to

30 about 2,000 V, preferably from about 50 to about 1,500V, more preferably ably from about 100 V to about 750 V, yet more preferably from about 200 V to about 300 V. The voltages used across gamma electrode 366 and

alpha, beta or delta electrodes 364, 365 or 367 when the pump is operated in

d.c. mode are typically from about 40 V to about 2,000 V, preferably from

about 50 to about 1,500V, more preferably ably from about 100 V to about

˜750 V, yet more preferably from about 200 V to about 300 V. The voltages

5   used across alpha and beta electrodes 364 and 365 when the pump is

operated in pulsed mode can be as indicated above for d.c. mode, but are

typically from about 50 V to about 1,000 V, preferably from about 100 V and

about 400 V, more preferably from about 200 V to about 300 V. The

voltages used across gamma electrode 366 and the alpha, beta or gamma

10   electrode 364, 365 or 367 when the pump is operated in pulsed mode can be

as indicated above for d.c. mode, but are typically from about 50 V to about

1,000 V, preferably from about 100 V and about 400 V, more preferably

from about 200 V to about 300 V. Preferably, the ratio of pumping to

current will be such that no more than about one electron flows into the

15   solution adjacent to a first pump 360 or second pump 361 for every 1,000

molecules that move past the pump 360 or 361, more preferably for every

10,000 molecules that move past the pump 360 or 361, yet more preferably

for every 100,000 molecules that move past the pump 360 or 361.

           It is believed that an electrode-based internal pumping

20   system can best be integrated into the liquid distribution system of the

invention with flow-rate control at multiple pump sites and with relatively less

complex electronics if the pumps are operated by applying pulsed voltages

across the electrodes. Figure 1 shows an example of a pulse protocol where

the pulse-width of the voltage is r_1 and the pulse interval is r_2. Typically, r_1

25   is between about 1 μs and about 1 ms, preferably between about 0.1 ms and

about 1 ms. Typically, r_2 is between about 0.1 μs and about 10 ms,

preferably between about 1 ms and about 10 ms. A pulsed voltage protocol

is believed to confer other advantages including ease of integration into high

density electronics (allowing for hundreds of thousands of pumps to be

30   embedded on a wafer-sized device), reductions in the amount of electrolysis

that occurs at the electrodes, reductions in thermal convection n ar the

electrodes, and the ability to use simpler drivers. The pulse protocol can also

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use pulse wave geometries that are more complex than the block pattern illustrated in Figure 1.

Another, procedure that can be applied is to use a number of electrodes, typically evenly spaced, and to use a travelling wave protocol that

5   induces a voltage at each pair of adjacent electrodes in a timed manner that first begins to apply voltage to the first and second electrodes, then to the second and third electrodes, and so on. Such methods are described in Fuhr et al., *J. Microelectrical Systems*, 1: 141-145, 1992. It is believed that travelling wave protocols can induce temperature gradients and corresponding

10   conductivity gradients that facilitate electric field-induced fluid flow. Such temperature gradients can also be induced by positioning electrical heaters in association with the electrode-based first pumps 360 and second pumps 361.

While not wishing to be restricted to theory, several theoretical concepts are believed to play a role in the mechanics of EHD

15   pumping. The forces acting on a dielectric fluid are believed to be described by:

$$\vec{F} = q\vec{E} + \vec{P}\cdot\nabla\vec{E} - \tfrac{1}{2}E^2\nabla\epsilon + \nabla\left[\tfrac{1}{2}\rho\frac{\partial\epsilon}{\partial\rho}E^2\right]$$

20

where F is the force density, q is the charge density, E is the applied field, P is the polarization vector, ϵ is the permittivity and ρ is the mass density. Of the terms in the equation, the first and third are believed to be the most significant in the context of EHD pumping of fluids. The first term (qE) relates

25   to the Coulomb interaction with a space-charge region. The third term ($\tfrac{1}{2}E^2\nabla\epsilon$) relates to the dielectric force which is proportional to the gradient in permittivity.

In low fields, i.e., the Ohmic region where current is linearly proportional to voltage, the primary source of charges that will be acted upon

30   by the electric field are believed to be primarily due to ions from additives, ions from impurities and ions f rmed by autodissociation of molecules in the fluid. In intermediate fields, i.e. from beyond the Ohmic region t about 2

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V/μm, the charges are believed to be primarily formed by dissociation and electrolytic processes in the fluid. In higher fields, the charges are believed to be determined by injection processes at the electrodes, which electrodes inject homocharges.

5   For the purposes of this application, positive (+) flow shall be flow in the direction of the negative electrode, and negative (-) flow shall be flow in the direction of the positive electrode.

In a preferred embodiment of the invention, the controller 10 has a device for storing data and stores the values of voltage and polarity

10   suitable for pumping a number of solvents.

Experimental results indicate that the properties of fluid flow (like direction of flow) correlate well with the solvent's ability to stabilize and solvate the charged species injected or induced from the electrodes. The direction of flow is believed to be determined by the preference of the solvent

15   to solvate either cations or anions. This solvation preference is believed to imply a greater shell of solvent molecules that will be dragged in an electric field, creating fluid movement, when a field is applied to the electrodes of a first pump 360 or a second pump 361. For example, a preferred solvation of cations correlates with a preference for fluid flow from the anode to the

20   cathode (i.e., the positive direction). The degree of such a solvation preference for a solvent is believed to depend on the ability of the molecules within the solvent to accept or donate hydrogen bonds. In one aspect of the invention, for liquids whose pumping behavior has not yet been characterized, the controller will store initial pumping parameters estimated using on the

25   Linear Solvation Energy relationships established by R.W. Taft and co-workers. See, Kamlet et al., *J. Org. Chem.*, 48: 2877-2887, 1983 and Kamlet et al., *Prog. Phys. Org. Chem.*, 13: 485, 1981. These workers have categorized solvents in terms of the following parameters: π, the ability of the solvent to stabilize a stabilize a charge or dipole by virtue of its dielectric

30   properties; α, the hydrogen bond donating ability of the solvent; and β, the hydrogen bond accepting ability of the solvent. These parameters are more fully defined in th above-cited Kamlet et al. publications.

15

Using a one mm capillary of circular cross-section, a pair of
50 micron rod-shaped, platinum electrodes perpendicularly inserted to a depth
of 500 microns into the capillary with a 500 micron separation powered by a
400 V field, the direction of flow was determined for several solvents. The
5   direction of flow and the a, β, π, ϵ and dipole moment values are as follows:

Solvent	direction	a	β	π	ϵ	dipole moment
ethanol	-	0.83	0.77	.54	24.55	1.69
tetrahydro-furan	+	0	0.55	.58	7.58	1.75
chloroform	-	0.44	0	.58	4.806	1.01
acetone	+	0.08	0.48	.71	20.7	2.69
methanol	-	0.93	0.62	.6	32.7	2.87
2-propanol	+/-	0.76	0.95	.48	19.92	1.66
acetonitrile	+	0.19	0.31	.75	37.5	3.92
N-methyl-pyrrolidone	+	0	0.77	.92	32.0	4.09
diethyl ether	+	0	0.47	0.27	4.335	1.15
1,2 dichloro ethane	-	0	0	0.81	10.36	1.2
DMF	+	0	0.69	.88	36.71	3.86

It is believed that the a and β values reflect the ability of the
solvent under an electric field to solvate a negative or positive charged
species, with the magnitude of a - β correlating with (-) flow, and the
25   magnitude of β - a correlating with (+) flow. According to one aspect of the
invention, the preferred direction of flow of a liquid can be reversed from that
predicted as above if the fluid has a difference in a and β values that is small
but not zero and the electrode pair used creates an asymmetric field, such
that the acting force on either positive or negative charged species is
30   enhanced. One such electrode pair has an alpha electrode 364 with that
points in the directi n of intended flow and a beta electrode 365 that lines the
walls of the channel in which it is located. Preferably, th alpha electrode

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364 sufficiently points in the direction of flow such that its point defines a line that intersects the plane defined by the beta electrode 365. Preferably, the alpha electrode 364 ends in a point or wedge shape. Such an electrode-based pump, fabricated in a 1 mm capillary, has been shown to be

5   effective to pump 2-propanol in the direction pointed to by the alpha electrode 364 either when the voltage applied to the electrodes implied a (-) direction of flow or, with somewhat weaker flow, when the voltage applied to the electrodes implied a (+) direction of flow.

The asymmetric, electrode-based pump effective to pump 2-

10   propanol in the direction pointed to by the alpha electrode 364 is illustrated in Figure 2A. Alpha electrode 364 points from left to right in the figure. Beta electrode 365 is a ring electrode that is flush with the sides of the capillary 501. Using the QuickField program available from Tera Analysis, Granada Hills, CA, the electric field strengths and orientations at various points about

15   the electrodes is indicated by the size and orientation of the arrow at that point. It can be seen from Figure 2A that where alpha electrode 364 acts as a cathode, the area where a solvated negative ion would be influenced by a strong field pushing it in the (+) direction is greater than the area where a strong field would push a solvated positive ion in the (-) direction. The

20   integration of these forces acting on these solvation spheres explains why asymmetric fields can be used to pump a liquid against its ordinary preferred direction of flow. Thus, depending on the liquids to be pumped, asymmetric fields can be used to assure a given direction of flow.

For comparison purposes, Figure 2B shows the field strength

25   and orientation of a number of points about a more symmetrical pump having alpha electrode 364 and beta electrode 365.

The pumping parameters of a liquid can be calibrated using a plug of the liquid disposed in a capillary that has an electrode-based pump and is angled uphill. If optical devices are associated with the capillary for

30   monitoring the position of the plug, the velocity of pumped flow uphill and the velocity of gravity driven downhill motion can be measured. With these velocities and the angle of the capillary, the pressure applied to the liquid can

be calculated. (Fluid resistance, $R = (8 \circ \mu \circ l)/\pi r^4$, where μ defines viscosity

and l = the length of the fluid plug; Pressure, $P = RA(v_{up} - v_{down})$, where A

= cross-sectional area). The efficiency of the pump can also be calculated (η

= $(q \circ \rho \circ Q \circ N_A)/m \circ l$, where q = charge of e⁻, p = density of liquid, Q = flow

5   rate = $v_{up} \circ A$, m = mass of liquid, and I = current). The velocities can be

measured with multiple single point observations of the location of either the

front or rear interfaces of the plug using fixed LEDs and optical detectors or in

a continuous mode using a light and a silicon photodiode position sensor,

such as a SL15 or SC10 position sensor available from UDT Sensors, Inc.,

10   Hawthorne, CA. With the latter method, the correlation between the signal

produced at the difference amplifier connected to the position sensor must be

calibrated prior to experimental use.

Figure 3 shows a calibration device having first optical

detector 401, second optical detector 402 and third optical detector 403.

15   These are preferably photodiodes such as the OTS-254 phototransister

available from Opto Technology, Inc., Wheeling, IL. Not shown are

corresponding first light source 411, second light source 412 and third light

source 413. These are preferably LEDs such as the Super Bright LEDs

available from Radio Shack. A capillary 420 is situated in mount 430. Mount

20   430 can be manipulated to orient capillary 420 at an angle offset from a

horizontal orientation. First lead 441 and second lead 442 relay voltage to

the electrode based pump 460 (obscured by mount 430) from the voltage-

generating portion 470 of controller 10. Electrical signals correlating with

light detection are relayed to the signal processing portion 480 of controller

25   10 by way of first data lead 481, second data lead 482 and third data lead

483. In operation, the signals from first optical detector 401, second optical

detector 402 and third optical detector 403 will show a transition point when

the interface of a plug 11 of liquid in capillary 420 goes by the respective

detector (401, 402 or 403). The timing of these transitions provides a

30   measure of the velocity of movement of the plug 11.

Figure 4 shows a calibration device having a position sensor

490 which generates el ctrical signals bas d on the distribution of light from

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light source 491 that impacts the surface of the position sensor 490. Light

source 491 has a power source 492. Leads 440 that relay voltage to pump

460 are shown schematically. The voltage is controlled by the controller 10

through its pulse generator 471 and voltage driver 472. Electrical output

5   from the position sensor is relayed via leads 484 to the data acquisition

module 485 of controller 10. It will be recognized that the signal from the

position sensor can be calibrated so that it can be processed to determine the

position of the interface of plug 11. This information can be used to

calculated the velocity of the movement of plug 11.

10   The pumping parameters for a number of solvents have been

determined in the 1 mm capillary described above, as follows:

Solvent	Flow rate, Q μl/sec	Pressure, P N/m^2	electrical efficiency, η, molecules/e$^-$
acetone	14.56	16.33	1.9×10^6
methanol	24.46	26.32	9.7×10^4
1-propanol	16.39	74.89	4.2×10^5
diethyl ether	18.44	20.45	5.8×10^8
1,2 dichloroethane	14.24	46.55	2.9×10^7

            Another aspect of pumping is the observation that fluids that

20   are resistant to pumping at a reasonable field strength can be made more

susceptible to electrode-based pumping by adding a suitable pumping

additive. Preferably, the pumping additive is miscible with the resistant fluid

and can be pumped at high pressure, P, high flow rate, Q, and good electrical

efficiency, η (i.e., molecules pumped per electron of current). Generally, the

25   pumping additive comprises from about 0.05 % w/w to about 10 % w/w of

the resulting mixture, preferably from about 0.1 % w/w to about 5 % w/w,

more preferably from about 0.1 % w/w to about 1 % w/w. Carbon

tetrachloride and cyclohexane do not pump using the electrode pump situated

in a capillary described above at a voltage of 2,000 V. By adding 0.5 % w/w

30   acetone or methanol as a pumping additive, both of these fluids can be

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pumped at a voltage of 1,000 V. In some cases, it is desirable to reverse the preferred flow direction of a liquid by mixing with it a pumping additive that strongly pumps in the desired direction. In all cases, pumping additives are selected on the basis of their pumping characteristics and their compatibility

5   with the chemistries or other processes sought to be achieved in the liquid distribution system.

7   The electrode-based pumps of the invention can be operated to as a valve to resist flow in a certain direction by operating the pumps to counter the unwanted flow. To power the electrode-based pumps, one or

10   more digital drivers, consisting of, for example, a shift register, latch, gate and switching device, such as a DMOS transistor, permits simplified electronics so that fluid flow in each of the channels can be controlled independently. Preferably, each digital driver is connected to multiple switching devices that each can be used to control the pumping rate of a

15   separate electrode-based pump, as illustrated in Figure 11. In Figure 11, data is input into shift register 50. The shift register 50 is connected to multiple electrode-based pumps 360 or 361 via a pathway that includes serially a latch, gate 56, and high voltage switching device 52. The latches are each connected to a latch signal input. The gates 56 are each connected to a gate

20   enabling input. The high voltage switching devices 52 are connected to a high voltage source via a pull-up resistor.

The invention includes employing an electrode-based pump to move reagent selected from the group consisting solutions of amino acids, protected amino acids, nucleotides, protected nucleotides, carbodiimides,

25   reactive derivatives of N-protected amino acids and phosphoamidite derivatives of nucleotides. The carbodiimides are preferably C2 to C12 aryl carbodiimides. The concentration of these reagents is preferably from about 0.01 M to about 0.2 M.

The invention further provides a method of pumping

30   comprising employing an electrode-based pump to move a reagent selected from the group consisting of organic amines, such as C1 to C10 hydrocarb ns substituted with an amino gr up and carboxylic acids, such as

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C1 to C10 hydrocarbons substituted with a carboxylic acid group. Preferably, the reagent is dissolved in a solvent. In another preferred embodiment, the solvent, in the absence of the reagent, does not pump using a d.c. powered electrode-based pump at a voltage of 2,000 V/mm, more preferably it does

5   not pump using a d.c. powered electrode-based pump at a voltage of 4,000 V/mm..

Features of other distribution systems described in this application can be applied to this embodiment, irrespective of under which subheading they are described.

10

B. Hydrologic Liquid Distribution System

One structure in which the invention is usefully employed is a hydrologic liquid distribution system made up of a number of reservoirs and a large number of reaction cells, wherein liquid from any given reservoir can be

15   systematically directed to all or a substantial subset of the reactor cells.

Such a liquid distribution system 100 is illustrated in Figures 5-10. The distribution system is formed of at least three plates, a feedthrough plate 300, a distribution plate 310 and a reaction cell plate 320 _ (Figure 5). The feedthrough plate 300 is bonded to the distribution plate 310.

20   Most importantly, the feedthrough plate 300 has multiple first electrodes 360 and second electrodes 361 that can be manufactured according to the invention. The reaction cell plate 320 is typically removably fitted to the underside of the distribution plate 310, or the underside of intermediate plate 330 interposed between the distribution plate 310 and the reaction cell plate

25   320.

Figure 6 shows the layout of a distribution plate 310. Figure 7 shows an expanded view of a portion of a distribution plate 310 that better illustrates some of the features obscured by the scale of Figure 6. Typically, the structures indicated in solid lines will be formed in the top layer of the

30   distribution plat 310, while the structures indicated with dotted lines will be formed in the bottom layer of the distribution plate 310, except that in Figure 6 th   reaction cells 350 are indicated by boxes in solid lin s even thought

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these structures are located in a lower plane . Where appropriate, vertical channels connect the structures in the top of the distribution plate 310 with those in the bottom. For convenience, the axis from the top of the illustration to the bottom is designated the NS axis, while the axis from right to left is
5   the EW axis.

At the top of Figure 6 are four first fluid reservoirs 200A, 200B, 200C and 200D, each having a defined fill level. Each of these first fluid reservoirs 200A, 200B, 200C and 200D has two first reservoir extensions 212 extending along substantially all of an EW axis of the
10 distribution plate 310. The ceilings of the first reservoir extensions 212 preferably are at substantially the same elevation as the first fill level. At five staggered locations, A1, B1, C1, D1 and E1, along the EW axis of the first reservoir extensions 212 there are four first vertical channels 214 (not shown) that connect the first reservoir extensions 212 with four first
15 horizontal feeder channel segments 216 that are formed in the bottom layer of the distribution plate 310. At each staggered location A1, B1, C1, D1 or .E1, four adjacent first horizontal feeder channel segments 216, which are connected to separate first reservoir extensions 212, extend along an NS axis to ten positions, A2, B2, C2, D2, E2, F2, G2, H2, I2 and J2. Each position
20 A2, B2, C2, D2, E2, F2, G2, I2 or J2 along the course of each such set of four adjacent horizontal feeder channel segments 216 is adjacent to a pair of reaction cells 350 (not shown). At these positions A2, B2, C2, D2, E2, F2, G2, H2, I2, or J2, the four adjacent first horizontal feeder channel segments 216 are separately connected, via separate second vertical channels 225 (see
25 Figure 8), to each of four perpendicular first distribution channels 222 formed in the top layer of the distribution plate 310. The ceilings of the first distribution channels 222 define a second fill level that is typically substantially the elevation of the first fill level. The fill level of a distribution channel (e.g., the second fill level) is "substantially" the fill level of the
30 connected r servoir (e.g., the first fill level) if they ar offset v rtically by no more than about 10% of the depth of the channel; ven if th fill levels are further offset vertically they are still substantially th sam if filling the

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reservoir to its fill level results in filling the connected distribution channel and the retention of fluid in the connected distribution channel (for instance, retention due to the capillary barriers described further below with reference to Figure 8). The combination of a first vertical channel 214, connected to a

5 horizontal feeder channel segment 216, in turn connected to a second vertical channel 225 makes up a first feeder channel 217 (not identified in the Figures).

If liquids are maintained at a defined first level in a first fluid reservoir 200, then substantially the same level will be maintained in the first

10 distribution channels 222 connected to that first fluid reservoir 200 via first feeder channels 217. This equalization occurs due to the principle that two connected bodies of liquid will tend to seek the same level and, where the size of the channels allows, due to capillary flow. Liquids are maintained at a defined level in the first fluid reservoirs. In the illustrated embodiment, liquid

15 is fed into the fluid reservoir 200 through channels in the feedthrough plate 300 and such liquid that is not needed to fill the fluid reservoirs to the defined level is drained through drains 380. First openings 381 (not shown) are formed in the bottom layer of the feedthrough plate 300 to create a liquid connection or sluice between the first fluid reservoirs 200 and the drains 380.

20 Liquids are constantly feed into the first fluid reservoirs 200 (as well as the second fluid reservoirs 210 and third fluid reservoirs 220) typically by the use of an external pump 15 (not shown), such as the model number 205U multichannel cassette pump available from Watson-Marlow, Inc. Alternatively, a defined level can be maintained by monitoring the level of

25 liquid in the first fluid reservoirs 200 (or second fluid reservoirs 210 or third fluid reservoirs 220) and only activating the pumps feeding liquid to a given fluid reservoir when needed to maintain the defined level.

Each set of four adjacent first distribution channels 222 are adjacent to two buffer channels 218, located to each side of the first

30 distribution channels 222 along the EW axis. Liquid can be pumped from any first distribution channel 222 into the adjacent buffer channel 218 by activating the first pump 360 (indicated in Figure 7 by two filled dots

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representing the electrodes of one type of pump) of the first distribution
channel 222. This pumping creates additional pressure that moves the liquid
over capillary barrier 370 (see Figure 8) separating the first distribution
channel 222 and the buffer channel 218. Between each first distribution
5   channel 222, second distribution channel 224 or third distribution channel
226 and the adjacent buffer channel 218 and between each buffer channel
218 and its adjacent third vertical channel 390 (described below) there is
such a capillary barrier 370 that inhibits liquid flow when the pumps are not
activated. Second openings 362 (see Figure 8) are formed in the bottom
10   layer of the feedthrough plate 300 to create a liquid connection or sluice
between the first distribution channels 222 and the buffer channels 218.
From a buffer channel 218, liquid can be pumped using a second pump 361
(indicated in Figure 8 by two filled dots representing the electrodes of one
type of pump) to a third vertical channel 390 that connects with a reaction
15   cell in the reaction cell plate 320. Third openings 363 (see Figure 8) in the
bottom layer of the feedthrough plate 300 or the distribution plate 310 serve
to create a liquid connection or sluice between the buffer channels 218 and
third vertical channels 390.

            Figure 8 illustrates a capillary barrier 370, at which a
20   meniscus 371 forms, at the junction between a first distribution channel 222
containing liquid 11 and either a buffer channel 218 or a third vertical channel
390. The meniscus 371 formed at the outlet of first distribution channel 222
into buffer channel 218 will tend to inhibit seepage from the first distribution
channel 222, such as the seepage that can result from capillary forces. In
25   some embodiments there are vents (not illustrated) that extend through the
feedthrough plate 300 at the tops of buffer channel 218 or third vertical
channel 390.

            Note that only a small cut-away of NS oriented horizontal
feeder channel segments 216 are shown in Figure 8. Typically, these
30   channels extend inwardly and outwardly from the illustrated cut-away and
connect with additional first distribution channels 222 situated to distribute
liquid to other reaction cells 350.

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Along the right side of the distribution plate 310 are ten second fluid reservoirs 210, each having a second reservoir extension 240 extending along an EW axis. Second distribution channels 224 form "L"-extensions off of second reservoir extensions 240 and are each

5   positioned adjacent to a separate buffer channel 218, such that there are ten second distribution channels 224 extending off of each second reservoir extension 240. Each second distribution channel 224 has a pump 360 that can move liquid from a second distribution channel 224 to the adjacent buffer channel 218. Second openings 362 (not shown) in the bottom of

10 feedthrough plate 300 serve to provide a sluice or route of liquid connection between the second distribution channels 224 and the buffer channels 218. Liquid moves from the buffer channels 218 to the reaction cells as described above. Located adjacent to each second reservoir 210 is a drain 380 (not shown) that operates to maintain a defined third fill level as described above.

15   As will be described further below in Section D in reference to Figures 9A - 9D, the capillary barriers 370 and sluices created by the second openings 362 or third openings 363 act as a combined valve and pump. The capillary barriers 370 prevent flow to the reaction cell, which flow would be favored by capillary forces, until the first pumps 360 or second

20 pumps 361 provide the extra pressure needed to overcome the capillary barriers 370. Narrowing the sluices can increase the capillary forces favoring flow, thereby reducing the amount of added pressure needed to overcome the capillary barriers 370. The use of the capillary barriers 370 allows flow control to be governed by the first pumps 360 or second pumps 361, which

25 are typically controlled by controller 10.

Located along the bottom edge of the distribution plate illustrated in Figure 6 are ten third liquid fluid reservoirs 220. Horizontal feeder channel segments 230 are connected to the third fluid reservoirs 220 and to third distribution channels 226 via fourth vertical channels 227. The

30 third distribution channels 226 have first pumps 360 which can move liquid into adjacent buffer channels 218 via penings 362 (not shown) in th fe dthrough plate 300. Located adjacent to each third fluid reservoir 220 is a

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drain 380 (not shown) that operates to maintain a defined fourth fill level as described above. Third fluid reservoirs 220 and connected third distribution channels 226 operate in just the same way as first fluid reservoirs 200 and first distribution channels 222. Those of ordinary skill in the art will readily

5   envision alternative geometries wherein a number of separate third fluid reservoirs 220 can interact with a given buffer channel 218 via a number of third distribution channels 226 positioned adjacent to the buffer channel 218. Located adjacent to each third reservoir 220 is a drain 380 (not shown) that operates to maintain a defined third fill level as described above.

10   The above discussion describes the distribution system as being formed with a feedthrough plate 300, distribution plate 310 and reaction cell plate 320. However, it will be clear that additional plates can conveniently be incorporated into the distribution system. For instance, a intermediate plate 330 is, in a preferred embodiment, permanently bonded

15   underneath the distribution plate 310 and interposed between the distribution plate 310 and the reaction cell plate 320. The use of the intermediate plate 330 allows for much greater flexibility in the design of the channels the form the distribution system.

20   C. Controller

            The controller 10 will typically be an electronic processor. However, it can also be a simpler device comprised of timers, switches, solenoids and the like. The important feature of controller 10 is that it directs the activity of the first pumps 360 and second pumps 361 and, optionally,

25   the activity of external pumps 171. A circuit of thin film transistors (not shown) can be formed on the liquid distribution system to provide power to the wells via leads and electrodes, and to connect them with the driving means such as the controller 10, so as to move liquids through the array. Pins can also be formed substrate which are addressable by logic circuits that

30   are connected t the c ntroller 10 for example.

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D. Capillary barriers

Capillary barriers have been described above with reference to Figure 8. However, more complex design considerations than were discussed above can, in some cases, affect the design of the capillary barrier.
5   In some cases it is desirable to narrow the sluice formed by second opening 362 or third opening 363 to increase the impedance to flow (i.e., the frictional resistance to flow) as appropriate to arrive at an appropriate flow rate when the associated first pump 360 or second pump 361 is activated. Such a narrowing is illustrated by comparing the sluice of Figure 9A with the
10   narrowed sluice of Figure 9D. The problem that this design alteration can create is that narrower channels can increase capillary forces, thereby limiting the effectiveness of channel breaks.

Thus, in one preferred embodiment, a channel break further includes one or more upwardly oriented sharp edges 369, as illustrated in
15   Figures 9B and 9C. More preferably, a channel break includes two or more upwardly oriented sharp edges 369. In Figure 9B, portion 362A of opening 362 is cut more deeply into first plate 300 to create an open space useful for the operation of upwardly oriented sharp edges 369.

20   ### E. Fabrication of Plates, Channels, Reservoirs and Reaction Cells

The liquid distribution systems of the invention can be constructed a support material that is, or can be made, resistant to the chemicals sought to be used in the chemical processes to be conducted in the device. For all of the above-described embodiments, the preferred support
25   material will be one that has shown itself susceptible to microfabrication methods that can form channels having cross-sectional dimensions between about 50 microns and about 250 microns, such as glass, fused silica, quartz, silicon wafer or suitable plastics. Glass, quartz, silicon and plastic support materials are preferably surface treated with a suitable treatment reagent such
30   as chloromethylsilane or dichlorodimethylsilane, which minimize the reactive sites on the material, including reactive sites that bind to biological molecul s such as proteins or nucleic acids. As discussed earlier, the expansion valve

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liquid distribution system is preferably constructed of a plastic. In embodiments that require relatively densely packed electrical devices, a non-conducting support material, such as a suitable glass, is preferred. Corning 211 borosilicate glass, Corning 7740 borosilicate glass, available

5   from Corning Glass Co., Corning, NY, are among the preferred glasses.

The liquid distribution system of the invention is preferably constructed from separate plates of materials on which channels, reservoirs and reaction cells are formed, and these plates are later joined to form the liquid distribution system. This aspect of the invention is described in some

10 detail with respect to the hydrologic liquid distribution system. Preferably, the reaction cell plate, e.g. reaction cell plate 320, is the bottom plate and is reversibly joined to the next plate in the stack. The other plates forming the distribution system, which preferably comprise two to three plates are preferably permanently joined. This joinder can be done, for instance, using

15 adhesives, such as glass-glass thermal bonding.

One preferred method of permanently joining the plates is to first coat the plate with a layer of glass glaze generally having a thickness between about 50 microns and about 500 microns, more preferably between about 75 microns and about 125 microns. The above thicknesses

20 contemplate that substantial amounts of channel structure will be formed in the glaze layer. Otherwise, the glaze generally has a thickness between about 1 microns and about 100 microns, more preferably between about 10 microns and about 25 microns. These methods are preferably applied to join glass plates. Suitable glazes are available from Ferro Corp., Cincinnati, OH.

25 The glazed plate is treated to create channels, reservoirs, or reaction cells as described below. The glazed plate is positioned against another plate, which preferably is not glazed, and the two plates are heated to a temperature of about the softening temperature of the glaze or higher, but less than the softening temperature for the non-glaze portion of the plates.

30 Another preferred meth d of permanently joining glass plates uses a field assisted thermal bonding process. It has now been discovered that glass-glass sealing using field assist thermal bonding is possible despite

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the low conductivity of glass if a field assist bonding material is interposed between the plates to be bonded.

To the top or bottom surface of one glass plate a layer of a field assist bonding material is applied. Preferably, the field assist bonding

5   material layer has a thickness between about 50 nm and about 1,000 nm, more preferably, between about 150 nm and about 500 nm. The field assist bonding material can be a material capable of bonding glass plates pursuant to the method described herein. Preferably, the field assist bonding material is silicon or silica. More preferably, the field assist bonding material is silicon.

10   The field assist bonding material can be applied to a plate, for instance, by chemical vapor deposition or by a sputtering process where surface molecules are emitted from a cathode when the cathode is bombarded with positive ions from a rare gas discharge and the surface molecules collide with and bond to a nearby substrate. Pursuant to the

15   present invention, silicon layers of between about 150 nm and about 500 nm thickness have been bonded to glass plates under conditions that can be expected to generate an outer surface layer of silicon dioxide, such as an about 20Å layer, although the sealing process is believed to be effective in the absence of this layer. The coated plate is treated, as needed, to create

20   channels, reservoirs, or reaction cells using the method described below. Alternatively, the plate was so treated prior to coating with the field-assist bonding material. The coated plate is then positioned against another plate, which preferably is not coated, and placed in a field assisted bonding device 700 such as that illustrated in Figure 9. The field assisted bonding device

25   700 has a heating device 710, such as a heating plate. The field assisted bonding device 700 further has an electrode 720 and a ground 730 that allows a voltage to be applied across the first plate 740 and the second plate 750, to which has been applied a layer of silicon 760. Generally, the field assisted bonding is conducted under a normal atmosphere.

30   The plates are brought to a temperature effective when an appropriate el ctric fi ld is applied across the plates ff ctive to accelerate the bonding process. While not wishing to be bound by theory, it is believed

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that the combination of a cathode applied to the first glass plate 740 and the greater exchange-site mobility of ions (such as sodium ions) caused by the elevated temperature causes an ion depletion on the face of the first glass plate 740 opposite that to which the cathode is applied. The ion depletion, it

5   is believed, causes a surface charge at the bottom surface of first glass substrate 740, which correlates with the creation of a strong localized electrostatic attraction for the second substrate 750. It is clear that this process creates strong bonding between the substrates and, it is believed that this is due to the formation of chemical bonds between the silica of the first

10   glass substrate 740 and the silicon coated onto the second glass substrate 750. Preferably, the temperature is brought to from about 200°C to about 600 °C, more preferably from about 300°C to about 450°C. During the process an voltage typically from about 200 V to about 2,500 V, preferably from about 500 V to about 1500 V, is applied across the first glass plate 740

15   and second glass plate 750. The voltage most suitably applied varies with the thickness of the glass plates. The voltage pulls the first glass plate 740 and second glass plate 750, including the silicon layer 760 applied to one of the plates, into intimate contact. Typically, hermetic sealing is achieved within minutes to about an hour, depending on the planar dimensions of the

20   glass plates. The time required to achieve adequate sealing varies with, among other things, the smoothness of the plates, the electrical field strength, the temperature, and the dimensions of the plates. Bonding between the plates is typically apparent visually, since it is accompanied by the disappearance of the interface between the plates and the formation of

25   gray color at the bonded regions that can be seen when an observer looks through the thinner dimensions of the two plates.

The method described above can be used to bond a glass substrate to another glass substrate and to a third glass substrate simultaneously.

30   Those of ordinary skill will recognize that while a hot plate is illustrated as providing the heating for the thermal assisted bonding, other heating d vic s, including ovens, may b used. It will also be realized that it is

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desirable to match, when possible, the coefficients of thermal expansion of the substrates to be bonded.

The reservoirs, reaction cells, horizontal channels and other structures of the fluid distribution system can be made by the following

5   procedure. A plate, that will for instance make up one of feedthrough plate 300, distribution plate 310, reaction cell plate 320 or intermediate plate 330, is coated sequentially on both sides with, first, a thin chromium layer of about 500 angstroms thickness and, second, a gold film about 2000 angstroms thick in known manner, as by evaporation or chemical vapor deposition

10   (CVD), to protect the plate from subsequent etchants. A two micron layer of a photoresist, such as Dynakem EPA of Hoechst-Celanese Corp., Bridgewater, NJ, is spun on and the photoresist is exposed, either using a mask or using square or rectangular images, suitably using the MRS 4500 panel stepper available from MRS Technology, Inc., Acton, MA. After development to form

15   openings in the resist layer, and baking the resist to remove the solvent, the gold layer in the openings is etched away using a standard etch of 4 grams of potassium iodide and 1 gram of iodine (I_2) in 25 ml of water. The underlying chromium layer is then separately etched using an acid chromium etch, such as KTI Chrome Etch of KTI Chemicals, Inc., Sunnyvale, CA. The plate is then

20   etched in an ultrasonic bath of $HF-HNO_3-H_2O$ in a ratio by volume of 14:20:66. The use of this etchant in an ultrasonic bath produces vertical sidewalls for the various structures. Etching is continued until the desired etch depth is obtained. Vertical channels are typically formed by laser ablation.

The various horizontal channels of the distribution system

25   embodiments typically have depths of about 50 microns to about 250 microns, preferably from about 50 microns to about 100 microns, more preferably from about 50 microns to about 80 microns. In an alternative embodiment, the preferred depths are from about 150 microns to about 400 microns. The widths of the horizontal channels and the diameters of the

30   vertical channels are typically from about 50 microns to about 200 microns, preferably from about 100 microns to about 200 micr ns, more preferably from about 120 microns to about 150 microns.

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F. Fabrication of Electrode-Based Pumps

In many embodiments, the liquid distribution systems of the invention require the formation of numerous electrodes for pumping fluids through the liquid distribution system. These electrodes are generally
5 fabricated in the top glass plate of the liquid distribution system. Typically each pair of electrodes is closely spaced (e.g. 50 to 250 microns separation). The electrodes are fabricated with diameters of preferably about 25 microns to about 150 microns, more preferably about 50 microns to about 75 microns. In preferred embodiments, the liquid distribution system has 10,000
10 reaction cell 350 with each reaction cell 350 having 6 - 10 associated electrode-based pumps. Thus, a liquid distribution system can require about 200,000 to about 300,000 electrodes. To produce such structures using mass production techniques requires forming the electrodes in a parallel, rather than sequential fashion. A preferred method of forming the electrodes
15 involves forming the holes in the plate (e.g., feedthrough plate 300) through which the electrodes will protrude, filling the holes with a metallic thick film ink (i.e., a so-called "via ink", which is a fluid material that scinters at a given temperature to form a mass that, upon cooling below the scintering temperature, is an electrically conductive solid) and then firing the plate and
20 ink fill to convert the ink into a good conductor that also seals the holes against fluid leakage. The method also creates portions of the electrodes that protrude through the plate to, on one side, provide the electrodes that will protrude into the liquids in fluid channels and, on the other side, provide contact points for attaching electrical controls.
25   For example, holes are drilled in 500 micron thick plates of borosilicate glass using an excimer laser. Holes having diameters between 50 and 150 microns are then filled with thick film inks, using an commercial Injection Via-fill Machine (Pacific Trinetics Model #VF-1000, San Marcos, CA). It has been unexpectedly discovered that only select formulations of via
30 inks sufficiently function to fill such high aspect ratio holes such that the fired ink adheres to the sides of the holes, d es not crack during the firing process, and seals the holes against fluid flow. One parameter that is important to so

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forming sealed, conductive conduits through high aspect holes is selecting
metal powder and glass powder components for the via ink that have
sufficiently fine dimensions. One parameter that is important to so forming
sealed, conductive conduits through high aspect holes is selecting metal
5 powder and glass powder components for the via ink that have sufficiently
fine dimensions. One suitable formulation uses: 12-507 Au powder (Technic
Inc., Woonsocket, RI), 89.3 % w/w; F-92 glass (O. Hommel Co., Carnegie,
PA), 5.7 % w/w; 15 % w/v ethyl cellulose N-300 (N-300, Aqualon,
Wilmington, DE) in Texanol™ (monoisobutarate ester of 2,2,4-trimethyl-1,3-
10 pentandiol, Eastman Chemical Products, Kingsport, TN), 2.4% w/w; 15 %
w/v Elvacite 2045™ (polyisobutyl methacrylate) in Terpineol T-318 (mixed
tertiary terpene alcohols, Hercules Inc., Wilmington, DE), 2.1 % w/w; and
Duomeen TDO™ (N-tallow alkyl trimethylenediamine oleates, Akzo
Chemicals, Chicago, IL), 0.5 % w/w. The gold powder from Technic, Inc.
15 has an average particle diameter of 0.9 microns. Another suitable formulation
uses: Ag Powder Q powder (Metz, South Plainfield, NJ), 80.8 % w/w; F-92
glass (O. Hommel Co. Carnegie, PA), 5.2 % w/w; VC-1 resin (37% w/w
Terpineol T-318, 55.5% w/w butyl carbitol, 7.5% w/w ethylcellulose N-300,
Aqualon, Wilmington, DE), 3.7 % w/w; 15 % w/v ethyl cellulose N-300 in
20 Texanol™, 4.0% w/w; 15 % w/v Elvacite 2045™ (polyisobutyl
methacrylate) in Terpineol T-318, 4.1 % w/w; Duomeen TDO™, 0.6 % w/w;
and Terpineol, ᵇ.6 % w/w. These formulations were fired at 550°C to form
high aspect ratio conductive conduits.

When the size of the glass or metal powders increases, good
25 filling properties (lack of cracking, good sealing against liquids, good
adherence to sides of hole) can often still be obtained by decreasing the
amount of organic in the via ink.

The devices used to insert via inks into holes in a plate
typically include a metal stencil with openings corresponding to the openings
30 in the plate. Via ink is applied above the stencil, which rests on the plate,
and a bladder device is used to pressurize the ink t force it to fill the holes.

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After filling, the plate with its via ink-filled holes is removed for further processing, as described below.

Prior to firing, much of the organic component is evaporated away by, for example, placing the ink-filled plate in a oven (e.g. at 100 °C)
5   for one to five minutes. Preferably, the firing is conducted at a temperature from about 450°C to about 700°C, more preferably from about 500°C.

Reagent	Flow direction*
4-(aminopropyl) morpholine	+
9-fluorenemethanol	+
p-nitrobenzyl alcohol	+
p-(methylthio) benzyl alcohol	-
o-aminobenzyl alcohol	+
2-methoxybenzyl alcohol	+.
2-(triflouromethyl) benzyl alcohol	+
2-amino-3-phenyl-1-propanol	+ P
diethylazodicarboxylate	- P
4-dimethylaminopyridine	+ P
carbazole	+
azobenzene	+
3,4-dihydroxybenzoic acid	- P
4-methylmorpholine N-oxide	+
3-cyanobenzoic acid	No flow
4-nitrophenylacetic acid	No flow, at 0.1M, flow occurs lower concentrations (0.01 - 0.1M)
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	No flow, at 0.1M, flow occurs lower concentrations (0.01 - 0.1M)
2,3-dichloro-5,6-dicyano-1,4-benzoquinone	+ weak
tetrapr pylammonium perruthenate	No flow

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Reagent	Flow direction[°]
l-oxo-2,2,6,6-tetramethylpiperdinium chloride	No flow
5-benzimidazolecarboxylic acid	N.D.[δ]
4-(aminomethyl) benzoic acid	N.D.
4-(aminomethyl) benzoic acid	N.D.
N,N-diisopropylethylamine	N.D.
isobuylamine	N.D.
glutathione (SH)	N.D.

[°] Those directional indicators (" + " or "-") followed by a "P" indicate that flow was achieved using a pulsed voltage program pursuant to Figure 1, where r_1 = 0.1 - 1 ms and r_2 = 3.0 - 10 ms.

[δ] "N.D.", in this table and the tables below, indicates either that the solute was immiscible with the solvent or that visual inspection suggested that it had decomposed.

The following solutions in DCM, at 0.1M unless otherwise indicated , have been tested:

Reagent	Flow direction[°]
allylamine	-
butylamine	-
cyclohexylamine	-
1-(3-aminopropyl) imidazole	-
diethylazodiacarboxylate	-
TP Palladium	-
isobutylamine	-
isoamylamine	-
propylamine	-

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1-(3-aminopropyl)imidazole	-
p-carboxybenzenesulfonamide	N.D.
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	N.D.

Those directional indicators (" + " or "-") followed by a "P" indicate that flow was achieved using a pulsed voltage program pursuant to Figure 1, where $r_1 = 0.1 - 1$ ms and $r_2 = 3.0 - 10$ ms.

The following solutions in methanol, all at 0.1M, have been tested:

Reagent	Flow direction*
4-fluorophenylacetic acid	-
9-fluorenemethanol	- P
p-(methylthio) benzyl alcohol	-
(R) sec-phenethyl alcohol	-
3-cyanobenzoic acid	No flow
4-nitrophenylacetic acid	- weak
allylamine	No flow
2-aminoethanol	No flow
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	N.D.
isobutylamine	N.D.
isomylamine	N.D.

Those directional indicators (" + " or "-") followed by a "P" indicate that flow was achieved using a pulsed voltage program pursuant to Figure 1, where $r_1 = 0.1 - 1$ ms and $r_2 = 3.0 - 10$ ms.

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Example 2 - An electrode-pump based preferential flow system

A channel system was fabricated on two inch by two inch by 20 mil plates of 211 Corning glass (Corning Glass Co., Corning, NY) to confirm that liquids can be switched to a desired flow pathway by controlling

5   the voltages applied to certain electrode-based pumps. As illustrated in Figures 11A and 11B, first channel 804 (2,600 μm long by 150 μm wide by 100 μm deep), second channel 805 (550 μm long by 100 μm wide by 100 μm deep), third channel 806 (800 μm long by 275 μm wide by 100 μm deep), fourth channel 807 (200 μm long by 100 μm wide by 100 μm deep), fifth

10 channel 808 (550 μm long by 100 μm wide by 100 μm deep) and sixth channel 809 (2,600 μm long by 150 μm wide by 100 μm deep) were fabricated on channel plate 810 (not shown). Also fabricated on the channel plate 810 were first well 800A, second well 800B and third well 800C, which were connected by the channels. An electrode plate 820 was overlaid and

15 sealed to the channel plate 810 by field assisted thermal bonding. The electrode plate 820 had openings into first well 800A and second well 800B (not illustrated). Third well 800C included a center drain 855. The electrode plate 820 further had platinum electrodes, fabricated by inserting 25 μm wires. The electrodes included first platinum electrode 801A, second

20 platinum electrode 801B, third platinum electrode 801C, fourth platinum electrode 802A, fifth platinum electrode 802B, third platinum electrode 802C, and the two electrodes comprising gamma electrode-based pump 803. First platinum electrode 801A, second platinum electrode 801B and third platinum electrode 801C make up alpha electrode-based pump 801, while fourth

25 platinum electrode 802A, fifth platinum electrode 802B and sixth electrode 802C make up beta electrode-based pump 802.

Figure 12A shows methanol flowing from first well 800A to second well 800B, while bypassing third well 800C. This is done by applying 160 V to alpha electrode-based pump 801. Figure 12B shows methanol

30 fl wing from second well 800B to third well 800C while bypassing first well 800A. This is done by applying 200 V to beta electr de-bas d pump 802, 100 V to gamma lectrode-based pump 803 and 120 V to alpha

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electrode-based pump 801, where the polarity at beta and gamma electrode-based pumps 802 and 803 favored flow into the third well 800C, and the polarity at alpha electrode-based pump 801 favored flow away from first well 800A.

5   **Example 3 - Electrode-based pumping past capillary barriers**

Figure 13 shows a prototype liquid distribution system fabricated pursuant to the hydrologic liquid distribution system. The distribution system was constructed from three plates of Corning 7740 borosilicate glass, Corning Glass, Inc., Corning, NY which plates became top

10   plate 910, intermediate plate 920 and bottom plate 930. The top of intermediate plate 920 was coated with silicon as described above. In top plate 910 were formed, by laser drilling, first hole 901A, second hole 901B, third hole 902A, fourth hole 902B, fifth hole 903A, sixth hole 903B, seventh hole 904A and eighth hole 904B, which holes each had a diameter of 75 μm.

15   First and second holes 901A and 901B were used to form first model electrode-based pump 961. Third and fourth holes 902A and 902B were used to form second prototype electrode-based pump 962. Fifth and sixth holes 903A and 903B were used to form third prototype electrode-based pump 963. Seventh and eighth holes 904A and 904B were used to form

20   fourth model prototype electrode-based pump 964. The electrodes in each of first through fourth prototype electrode-based pumps, 961 - 964, were separated by 200 μm. By etching, alpha opening 905, beta opening 906 and gamma opening 907 were formed on the underside of top plate 910. By laser drilling, ninth hole 908 and tenth hole 909, each with a diameter of 150 μm,

25   were formed through upper plate 910.

In intermediate plate 920 were formed first prototype channel 911 (made up of segments 911A - 911D) and second prototype channel 912 (made up of segments 912A - 912D). First and second prototype channels 911 and 912 having a depth of 80 μm and a width of

30   150 μm. The entri s into these two prototype channels 911 and 912 are provided by ninth hole 908 and tenth hole 909, resp ctiv ly. First reaction cell acc ss h le 913 and second reaction cell access hole 914, each with a

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diameter of 150 μm , were laser drilled through the intermediate plate 920. In the underside of intermediate plate 920, a delta opening 915 was formed, which delta opening 915 connects the reaction cell 950 to first and second prototype drain holes 921 and 922.

5   In the bottom plate 930, the reaction cell 950 was formed by etching. First prototype drain hole 921 and second prototype drain hole 922 were laser drilled through bottom plate 920. The top plate 910 and intermediate plate 920 were bonded together by field assisted thermal bonding.

10   When methanol was introduced into first prototype channel 911, the liquid was stopped from flowing into reaction cell access hole 913 by the capillary barrier formed by the structure at alpha opening 905. Correspondingly, the capillary barrier formed by the structure at beta opening 906 prevented methanol flow into the reaction cell access hole 914. Flow
15   into the reaction cell access holes 913 or 914, by either route, could be initiated by activating the appropriate pumps. For instance, to pump methanol through first prototype channel 911, first prototype electrode-based pump 901 and second prototype electrode-based pump 902 were biased by applying 200 V. Flow through the prototype channel 911 was observed.

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Reagent	Flow direction[°]
4-(aminopropyl) morpholine	+
9-fluorenemethanol	+
p-nitrobenzyl alcohol	+
p-(methylthio) benzyl alcohol	-
o-aminobenzyl alcohol	+
2-methoxybenzyl alcohol	+
2-(triflouromethyl) benzyl alcohol	+
2-amino-3-phenyl-1-propanol	+ P -
diethylazodicarboxylate	- P
4-dimethylaminopyridine	+ P
carbazole	+
azobenzene	+
3,4-dihydroxybenzoic acid	- P
4-methylmorpholine N-oxide	+
3-cyanobenzoic acid	No flow
4-nitrophenylacetic acid	No flow, at 0.1M, flow occurs lower concentrations (0.01 - 0.1M)
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	No flow, at 0.1M, flow occurs lower concentrations (0.01 - 0.1M)
2,3-dichloro-5,6-dicyano-1,4-benz oquinone	+ weak
tetrapropylammonium perruthenate	No flow
l-oxo-2,2,6,6-tetramethylpiperdini um chloride	No flow
5-benzimidazolecarboxylic acid	N.D.[6]
4-(aminomethyl) benzoic acid	N.D.
4-(aminomethyl) benzoic acid	N.D.
N,N-diisopropylethylamine	N.D.

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Reagent	Flow direction°
isobuylamine	N.D.
glutathione (SH)	N.D.

    ° Those directional indicators (" + " or "-") followed by a "P"

indicate that flow was achieved using a pulsed voltage

program pursuant to Figure 1, where r_1 = 0.1 - 1 ms and

r_2 = 3.0 - 10 ms.

    ᵟ "N.D.", in this table and the tables below, indicates either

that the solute was immiscible with the solvent or that visual

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TP Palladium	-
isobutylamine	-
isoamylamine	-
propylamine	-
1-(3-aminopropyl)imidazole	-
p-carboxybenzenesulfonamide	N.D.
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	N.D.

    ° Those directional indicators (" + " or "-") followed by a "P"

indicate that flow was achieved using a pulsed voltage

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program pursuant to Figure 1, where $r_1 = 0.1 - 1$ ms and $r_2 = 3.0 - 10$ ms.

The following solutions in methanol, all at 0.1M, have been tested:

Reagent	Flow direction[*]
4-fluorophenylacetic acid	-
9-fluorenemethanol	- P
p-(methylthio) benzyl alcohol	-
(R) sec-phenethyl alcohol	-
3-cyanobenzoic acid	No flow
4-nitrophenylacetic acid	- weak
allylamine	No flow
2-aminoethanol	No flow
2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)	N.D.
isobutylamine	N.D.
isomylamine	N.D.

[*] Those directional indicators (" + " or "-") followed by a "P" indicate that flow was achieved using a pulsed voltage program pursuant to Figure 1, where $r_1 = 0.1 - 1$ ms and $r_2 = 3.0 - 10$ ms.

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channel 808 (550 μm long by 100 μm wide by 100 μm deep) and sixth

channel 809 (2,600 μm long by 150 μm wide by 100 μm deep) were

fabricated on channel plate 810 (not shown). Also fabricated on the channel

plate 810 were first well 800A, second well 800B and third well 800C, which

5   were connected by the channels. An electrode plate 820 was overlaid and

sealed to the channel plate 810 by field assisted thermal bonding. The

electrode plate 820 had openings into first well 800A and second well 800B

(not illustrated). Third well 800C included a center drain 855. The electrode

plate 820 further had platinum electrodes, fabricated by inserting 25 μm

10   wires. The electrodes included first platinum electrode 801A, second

platinum electrode 801B, third platinum electrode 801C, fourth platinum

electrode 802A, fifth platinum electrode 802B, third platinum electrode 802C,

and the two electrodes comprising gamma electrode-based pump 803. First

platinum electrode 801A, second platinum electrode 801B and third platinum

15   electrode 801C make up alpha electrode-based pump 801, while fourth

platinum electrode 802A, fifth platinum electrode 802B and sixth electrode

802C make up beta electrode-based pump 802.

          Figure 12A shows methanol flowing from first well 800A to

second well 800B, while bypassing third well 800C. This is done by applying

20   160 V to alpha electrode-based pump 801. Figure 12B shows methanol

flowing from second well 800B to third well 800C while bypassing first well

800A. This is done by applying 200 V to beta electrode-based pump 802,

100 V to gamma electrode-based pump 803 and 120 V to alpha

electrode-based pump 801, where the polarity at beta and gamma

25   electrode-based pumps 802 and 803 favored flow into the third well 800C,

and the polarity at alpha electrode-based pump 801 favored flow away from

first well 800A.

Example 3 - Electrode-based pumping past capillary barriers

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plate 910, intermediate plate 920 and bottom plate 930. The top of
intermediate plate 920 was coated with silicon as described above. In top
plate 910 were formed, by laser drilling, first hole 901A, second hole 901B,
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5 hole 904A and eighth hole 904B, which holes each had a diameter of 75 μm .
First and second holes 901A and 901B were used to form first model
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holes 903A and 903B were used to form third prototype electrode-based

10 pump 963. Seventh and eighth holes 904A and 904B were used to form
fourth model prototype electrode-based pump 964. The electrodes in each of
first through fourth prototype electrode-based pumps, 961 - 964, were
separated by 200 μm . By etching, alpha opening 905, beta opening 906 and
gamma opening 907 were formed on the underside of top plate 910. By laser

15 drilling, ninth hole 908 and tenth hole 909, each with a diameter of 150 μm,
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        In intermediate plate 920 were formed first prototype
channel 911 (made up of segments 911A - 911D) and second prototype
channel 912 (made up of segments 912A - 912D). First and second

20 prototype channels 911 and 912 having a depth of 80 μm and a width of
150 μm . The entries into these two prototype channels 911 and 912 are
provided by ninth hole 908 and tenth hole 909, respectively. First reaction
cell access hole 913 and second reaction cell access hole 914, each with a
diameter of 150 μm , were laser drilled through the intermediate plate 920.

25 In the underside of intermediate plate 920, a delta opening 915 was formed,
which delta opening 915 connects the reaction cell 950 to first and second
prototype drain holes 921 and 922.

        In the bottom plate 930, the reaction cell 950 was formed by
etching. First prototype drain hole 921 and second prototype drain hole 922

30 were laser drilled through bottom plate 920. The top plate 910 and
intermediat plate 920 were bonded together by field assisted thermal
bonding.

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When methanol was introduced into first prototype channel 911, the liquid was stopped from flowing into reaction cell access hole 913 by the capillary barrier formed by the structure at alpha opening 905. Correspondingly, the capillary barrier formed by the structure at beta opening

5   906 prevented methanol flow into the reaction cell access hole 914. Flow into the reaction cell access holes 913 or 914, by either route, could be initiated by activating the appropriate pumps. For instance, to pump methanol through first prototype channel 911, first prototype electrode-based pump 901 and second prototype electrode-based pump 902 were biased by

10   applying 200 V. Flow through the prototype channel 911 was observed.

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IN THE CLAIMS:

1.   An electrode-based pump comprising a first electrode and a second electrode, wherein the first and second electrodes have a diameter from about 25 microns to about 100 microns and are spaced from
5   about 100 microns to about 2,500 microns apart.

2.   The electrode-based pump of claim 1, wherein the pump is situated in a fluid channel of capillary dimensions.

3.   The electrode-based pump of claim 1, wherein the first and second electrodes are from about 150 microns to about 1000 microns
10   apart.

4.   The electrode-based pump of claim 1, wherein the first and second electrodes are from about 150 microns to about 250 microns apart.

5.   An electrode-based pump comprising a first electrode,
15   second electrode and third electrode.

6.   The electrode-based pump of claim 1, wherein the pump is situated in a fluid channel of capillary dimensions.

7.   The electrode-based pump of claim 6, wherein the first and second electrodes are spaced from about 100 microns to about 2,500
20   microns apart, and wherein the third electrode is spaced from about 200 micron to about 5,000 microns from the first electrode and is closer to the second electrode.

8.   The electrode-based pump of claim 8, wherein the third electrode is spaced from about 500 micron to about 1,500 microns from
25   the second electrode.

9.   The electrode-based pump of claim 6, further comprising a fourth electrode.

10.   The electrode-based pump of claim 9, wherein the first and second electrodes shall be positioned between the third and fourth
30   electrodes, and wherein the third and fourth electrodes are spaced from about 200 micron to about 5,000 microns apart.

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11.   The electrode-based pump of claim 10, wherein the first and second electrodes are spaced from about 100 microns to about 2,500 microns apart.

12.   The electrode-based pump of claim 10, wherein the
5 third and fourth electrodes are spaced from about 500 micron to about 1,500 microns apart.

13.   A method of pumping comprising employing an electrode-based pump to move a reagent selected from the group consisting of organic amines and carboxylic acids.

10   14.   The method of claim 13, wherein the reagent is dissolved in a solvent.

15.   The method of claim 14, wherein the solvent, in the absence of the reagent, does not pump using d.c. powered electrode-based pumps at a voltage of 2,000 V/mm.

15   16.   The method of claim 15, wherein the solvent, in the absence of the reagent, does not pump using d.c. powered electrode-based pumps at a voltage of 4,000 V/mm.

17.   The method of claim 13, wherein the organic amines are C1 to C10 aryl amines and the carboxylic acids are C1 to C10 aryl
20 carboxylic acids.

18.   A method of pumping comprising employing an electrode-based pump to move reagent selected from the group consisting solutions of amino acids, protected amino acids, nucleotides, protected nucleotides, carbodiimides, reactive derivatives of amino acids and reactive
25 derivatives of nucleotides.

19.   A method of changing the electrokinetic pumping parameters of a liquid, the method comprising

(a)   selecting a pumping additive based on the pumping pressure, pumping flow rate and electrical efficiency exhibited by the additive,
30 and

(b)   mixing the pumping additive with the liquid to obtain a mixture having ither (i) improved pumping pressure, pumping flow rate or

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electrical efficiency, or (ii) having a preference for pumping in a direction
opposite that of the liquid, in the absence of pumping additive.

        20.   The method of claim 19, wherein the mixture obtained
has a flow preference opposite that of the liquid.

5   21.   The method of claim 19, wherein the mixture obtained
has improved pumping pressure, pumping flow rate or electrical efficiency.

        22.   The method of claim 19, wherein the pumping additive
comprises from about 0.05 % w/w to about 10 % w/w of mixture.

        23.   The method of claim 22, wherein the pumping additive
10 comprises from about 0.1 % w/w to about 5 % w/w of the mixture

        24.   The method of claim 23, wherein the pumping additive
comprises from about 0.1 % w/w to about 1 % w/w of the mixture.

        25.   An electrode-based pump situated in a fluid channel
comprising two or more electrodes, which pump can create an field such that
15 a liquid pumps in the direction opposite its flow preference.

        26.   The electrode-based pump of claim 25, comprising a
first electrode situated along the walls of the channel such that it defines a
plane intersecting the fluid channel and a second electrode oriented to point in
a direction that intersects the plane defined by the first electrode.

20   27.   The electrode-based pump of claim 26, wherein the
end of the second electrode is pointed or wedge-shaped.

        28.   A calibration device comprising

        (a)   a fluid channel of capillary dimensions,

        (b)   an electrode-based pump situated in the fluid channel,

25   (c)   a signal generating means for generating a signal
indicating the position of a moving plug of liquid situated in the fluid channel
either continuously or at two or more different times, and

        (d)   a calculating means for accepting the signal and
calculating the velocity of the fluid plug therefrom.

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29.   The calibration device of claim 28, further comprising
a means of positioning the fluid channel so that it is on a non-horizontal
plane.

30.   The calibration device of claim 29, wherein the
5   calculating means can calculate the pumping pressure based on the pumped
fluid velocity uphill and the gravitational velocity downhill.

31.   The calibration device of claim 29, further comprising
a liquid distribution system and a controller comprising an electrical data
storage device comprising a database of pumping programs for pumping one
10   or more liquids, wherein the values generated by the calibration device can be
stored in the database.

32.   A method of controlling electrokinetic pumping devices
comprising spaced electrodes in a channel having capillary dimensions
comprising:

15   a.   loading data directed to the applied voltage pulse with,
pulse repetition rate, electrode geometry and fluid properties into a computer

b.   converting the data to instructions for a digital driver
and transferring said instructions to said digital driver using a shift register;

c.   applying a latch signal to transfer data loaded into said
20   shift register; and

d.   applying the latch output signal and an enabling signal
of constant amplitude and variable pulse width and repetition rate to an AND
gate connected to a switching device, thereby controlling the flow of a fluid
in said channel.

25   33.   A method according to claim 32 wherein a plurality of
electrode pairs are connected through a switching device, an AND gate, and a
latch to said shift register and wherein the computer can apply instructions to
each switching device independently.
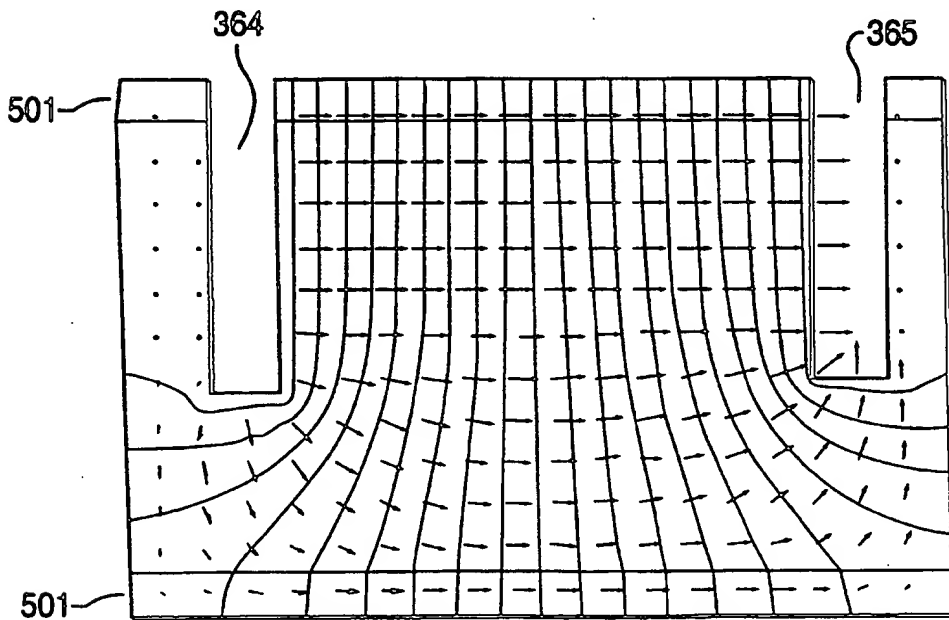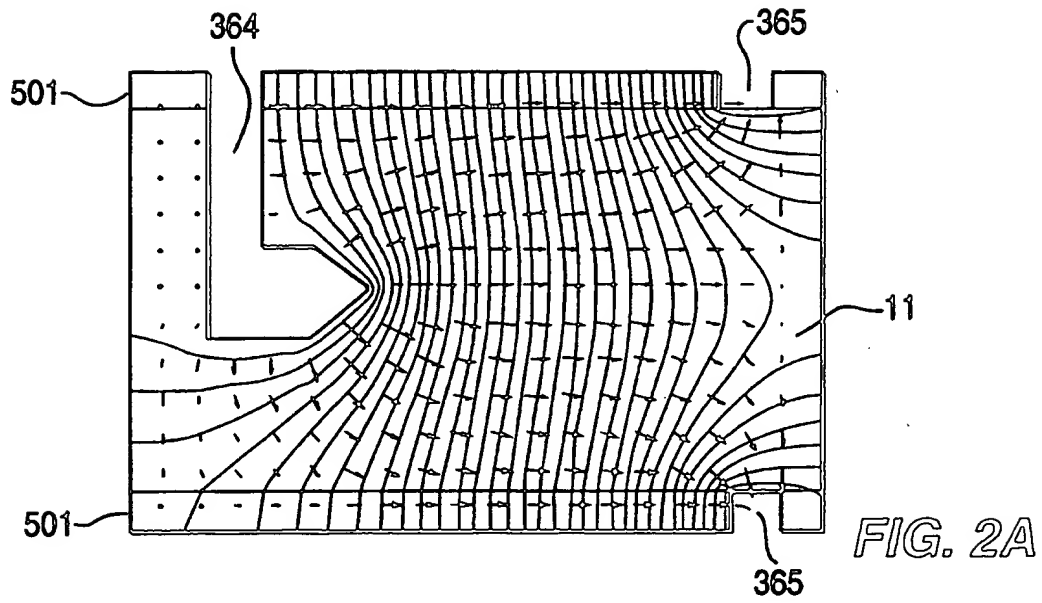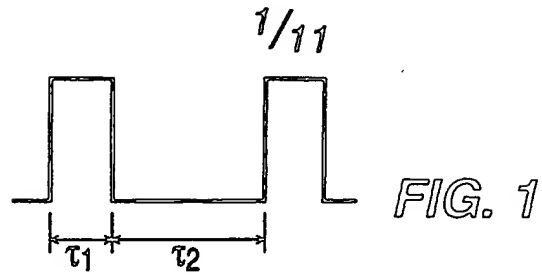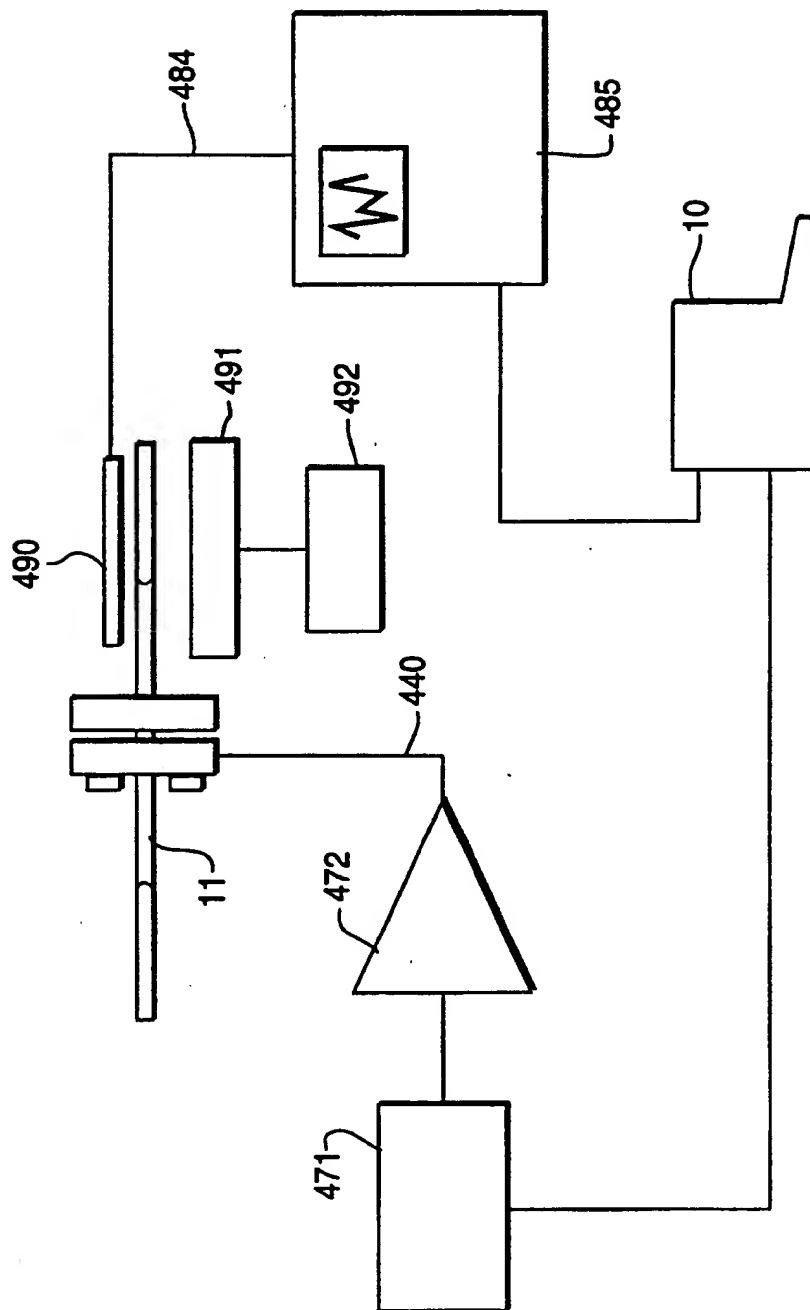
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FIG. 1

FIG. 2A

FIG. 2B

FIG. 3

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FIG. 4

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FIG. 5

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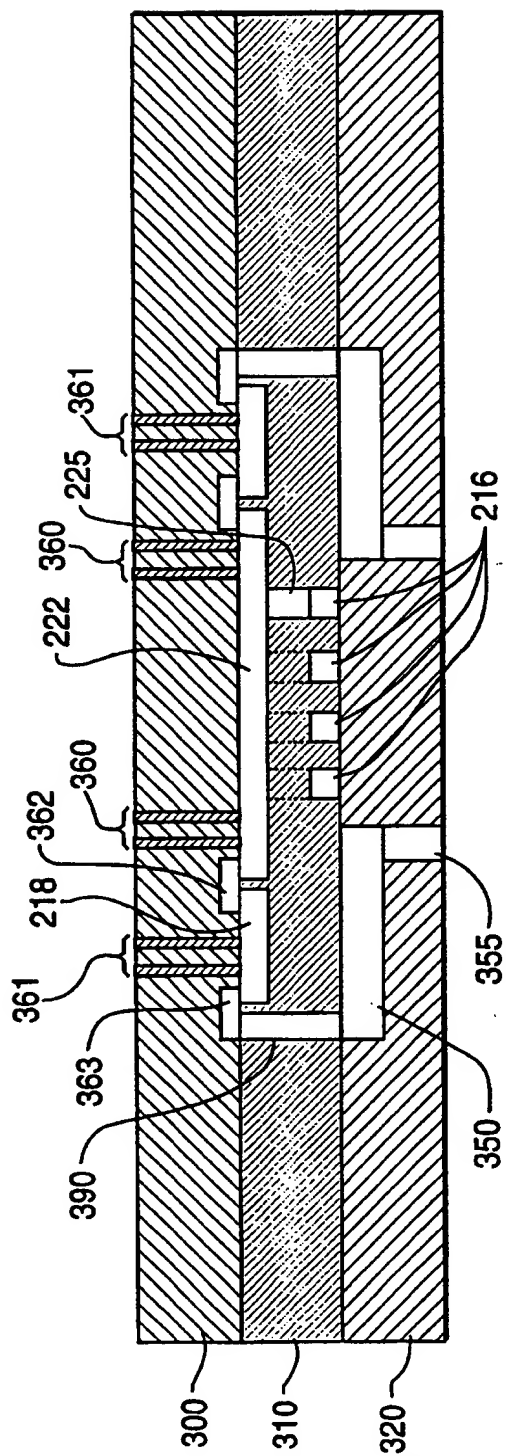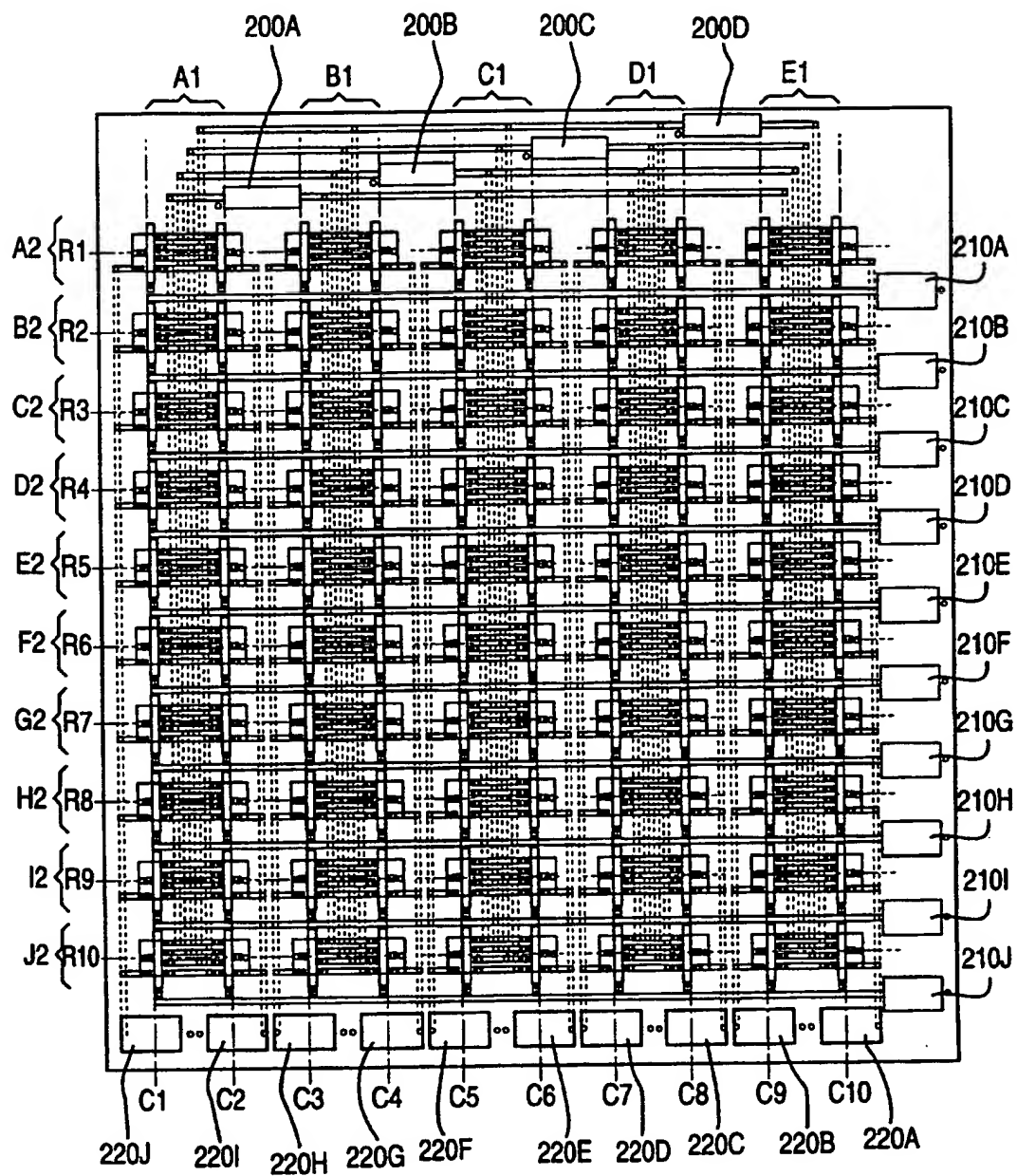
FIG. 6

FIG. 7
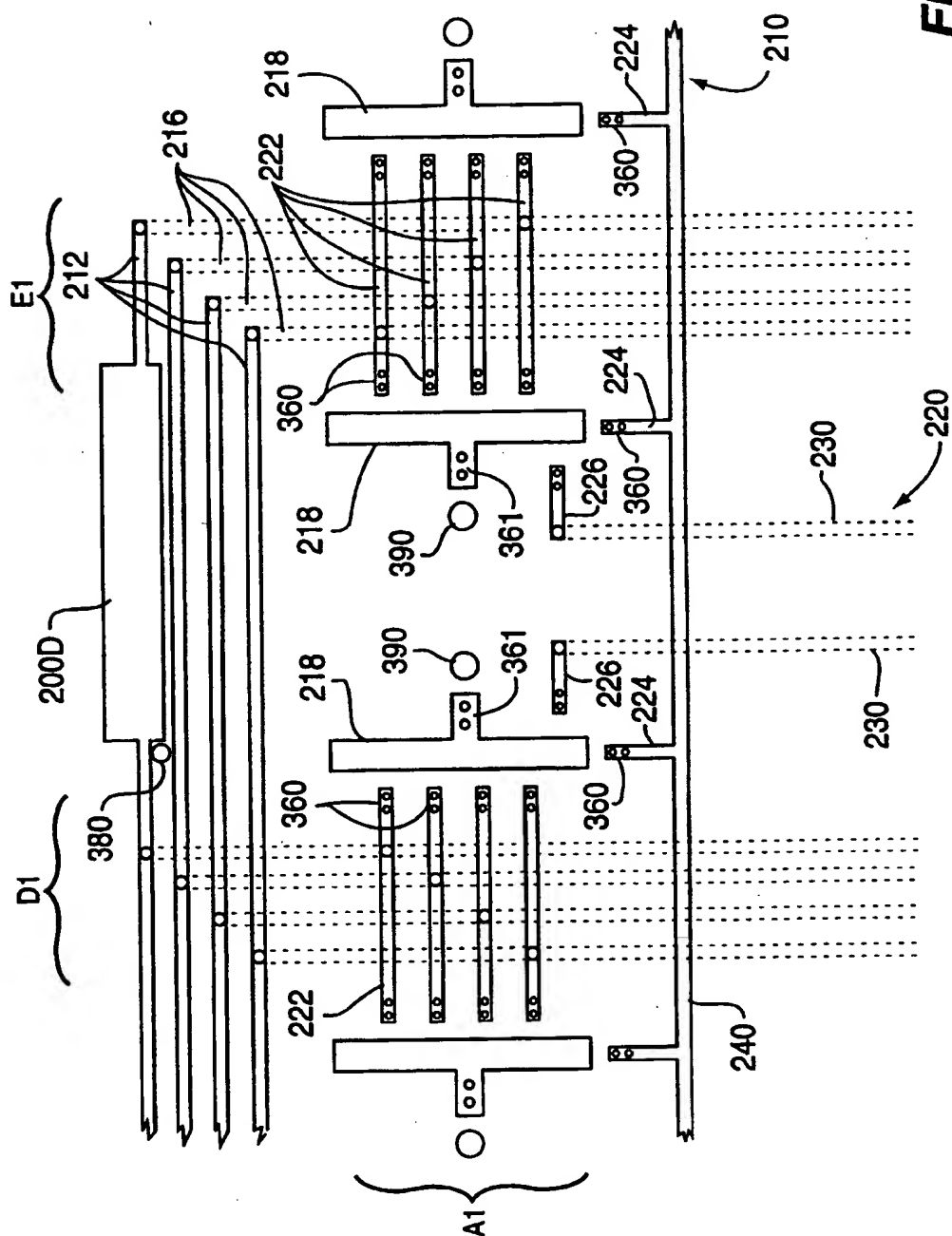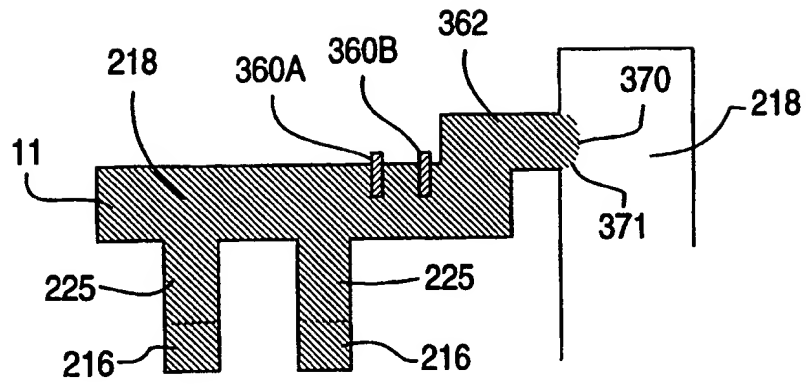
FIG. 8
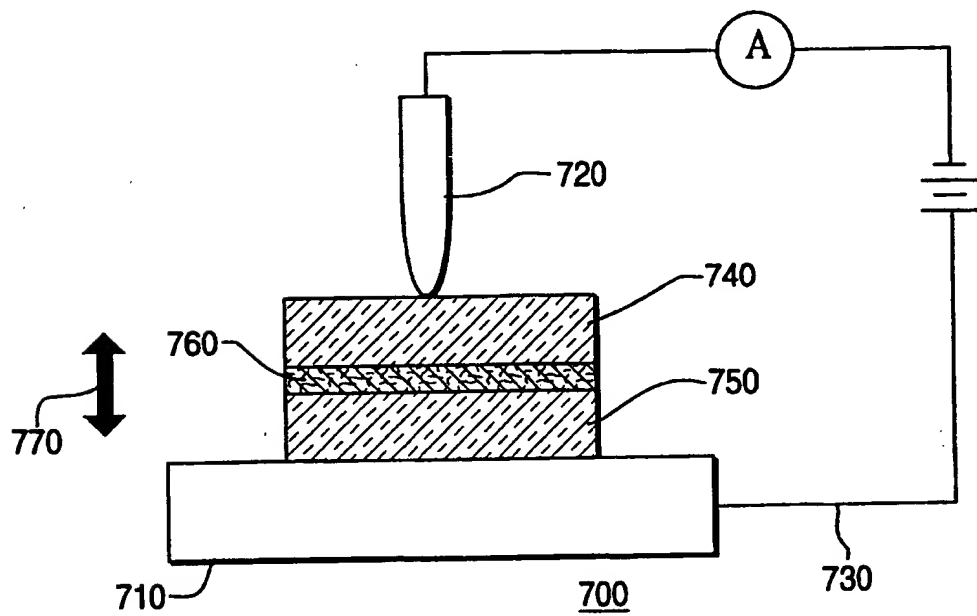
FIG. 10
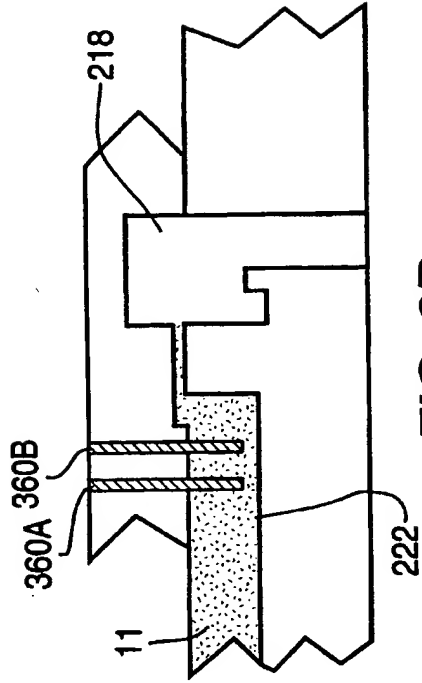
**FIG. 9D**
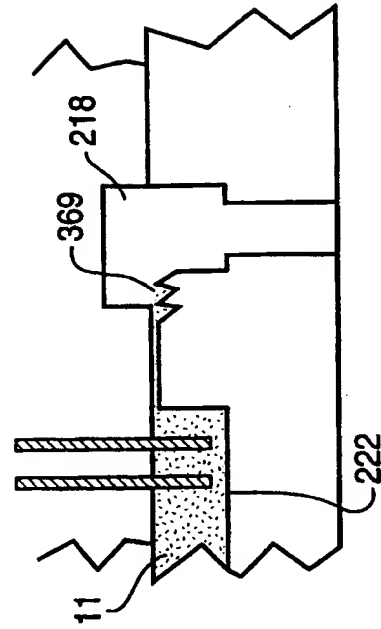
FIG. 9C
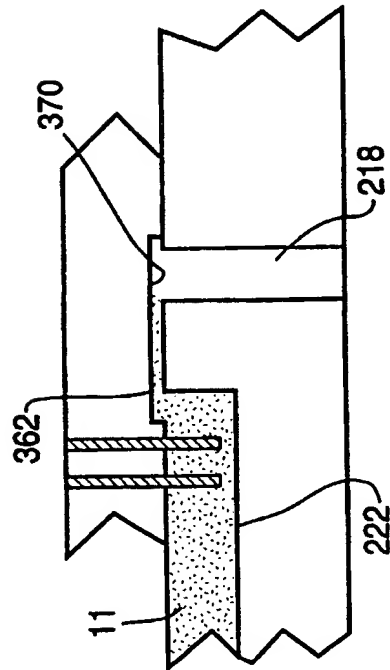
FIG. 9A
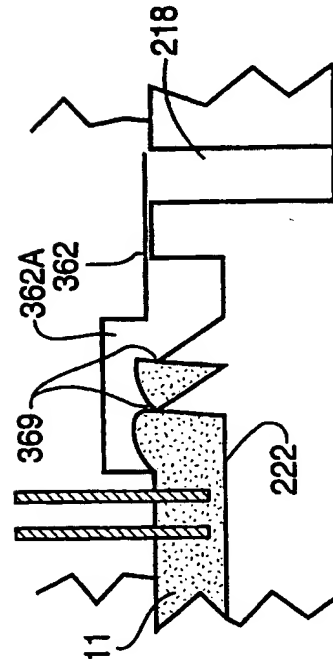
FIG. 9B

9/11
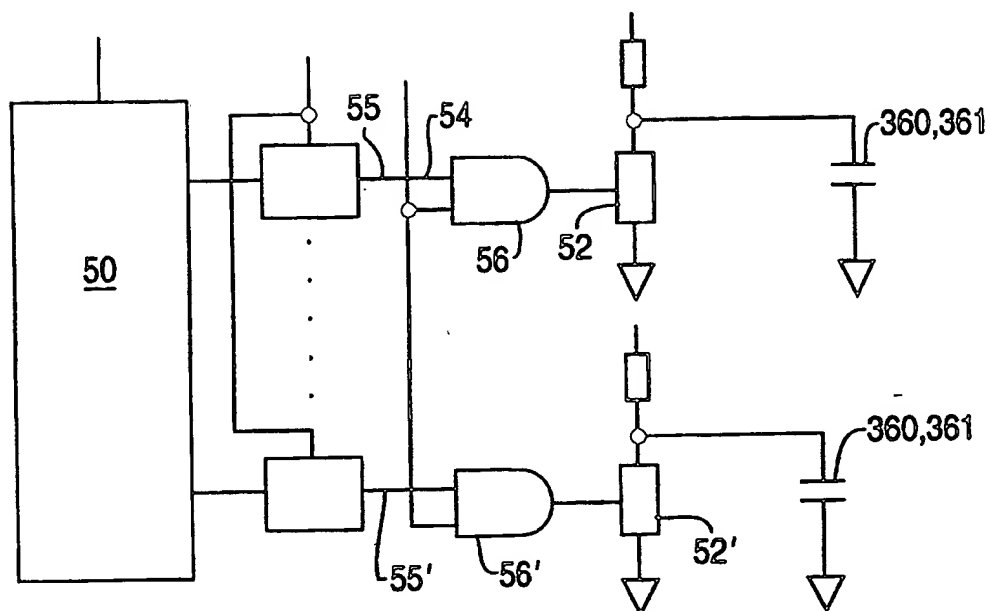
FIG. 11

FIG. 12A

FIG. 12B

SUBSTITUTE SHEET (RULE 26)
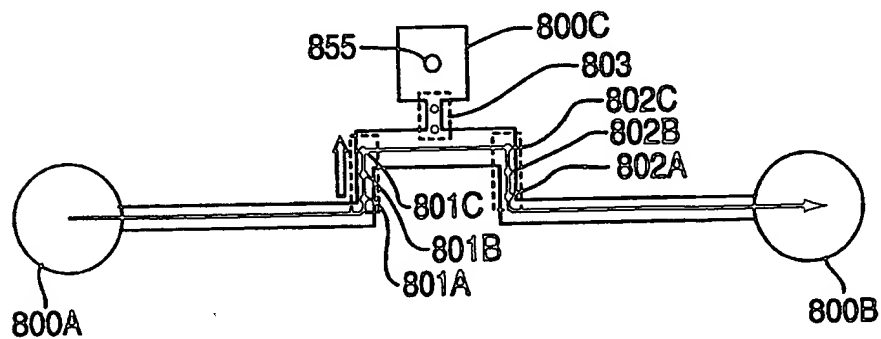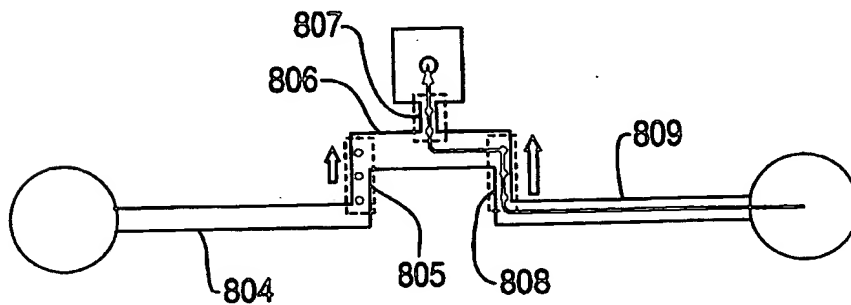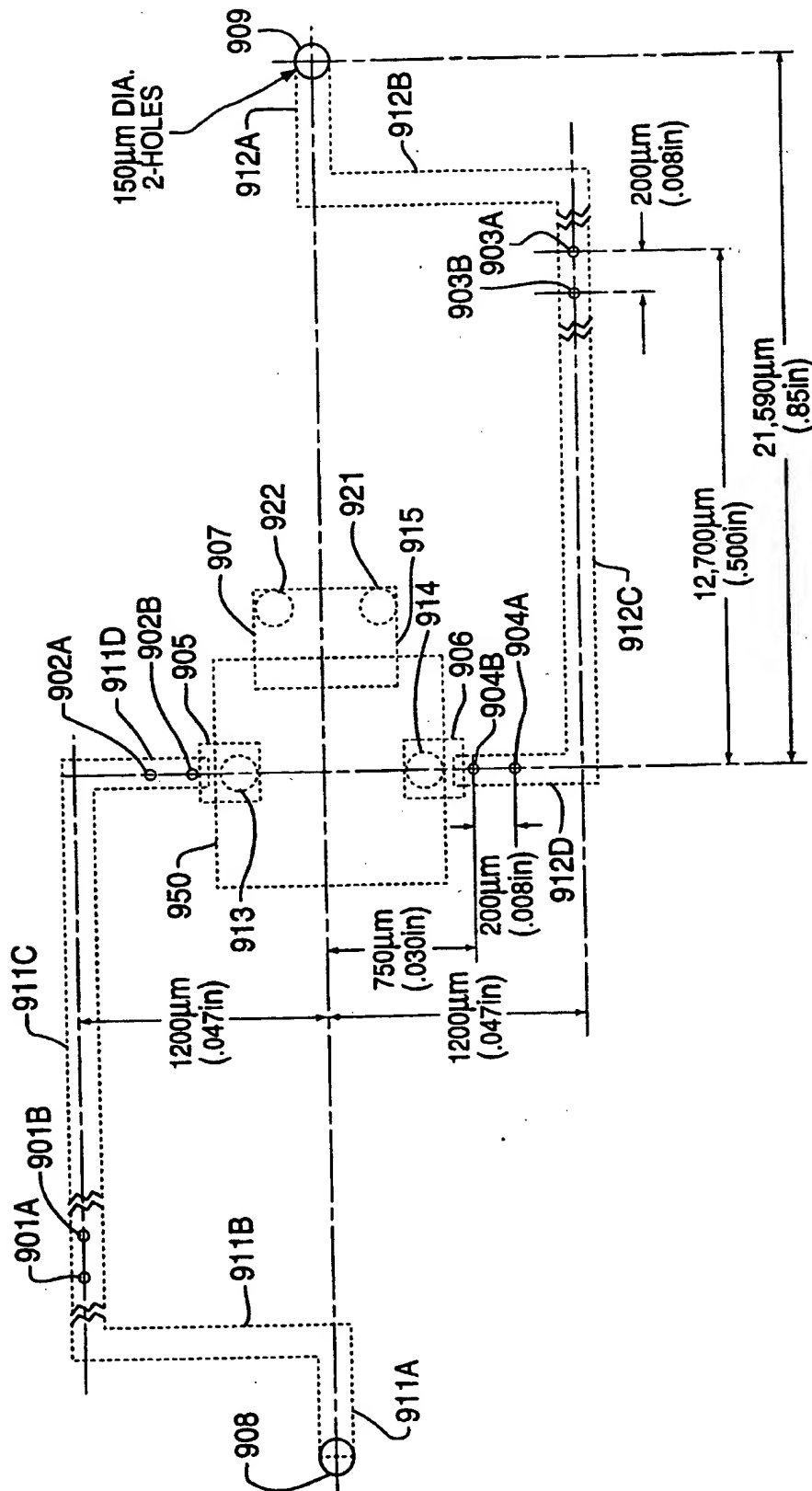
FIG. 13
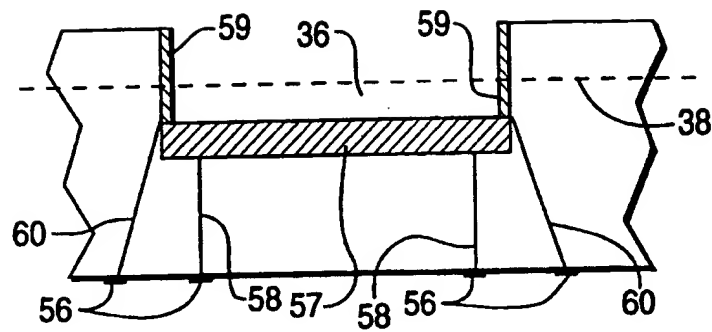
FIG. 14
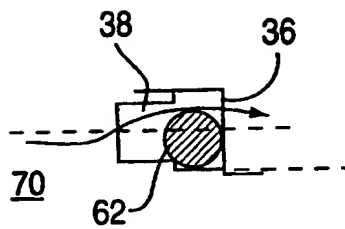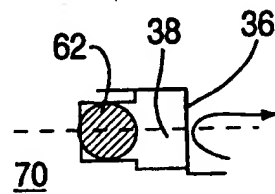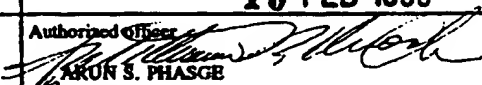
FIG. 15A   FIG. 15B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14586

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B03C 9/00; F04F 11/00; H02K 44/02
US CL :204/450,454,600,601; 417/48,49,50,53,54,55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 204/450,454,600,601; 417/48,49,50,53,54,55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,406,671 (ROZMUS) 27 SEPTEMBER 1983, SEE COLUMNS 3-6.	1-27.
Y	US, A, 2,715,190 (BRILL) 09 AUGUST 1955, SEE COLUMNS 1-4.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 JANUARY 1996	15 FEB 1996

Name and mailing address of the ISA/US	Authorized Officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ARUN S. PHASGE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

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